FACULDADE DE ODONTOLOGIA
PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA
CIRURGIA E TRAUMATOLOGIA BUCOMAXILOFACIAL

TESE DE DOUTORADO

EFEITOS DA SOLUÇÃO DE CARNOY NO REPARO ÓSSEO EM CAVIDADES EXPERIMENTAIS DE TÍBIAS DE RATOS

ANDRÉ TAKAHASHI
2008

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
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ANDRÉ TAKAHASHI

Tese apresentada à Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul, para obter o Título de Doutor, pelo Programa de Pós-Graduação em Odontologia.

Área de Concentração: Cirurgia e Traumatologia Bucomaxilofaciais.

Orientador: Prof. Dr. Rogério Miranda Pagnoncelli

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Dedico este trabalho as pessoas que...
Confiam em dias melhores,
Levantam a cabeça para o novo,
Acreditam no ser humano,
Unem sonhos e projetos de vida,
Insistem em esperar,
Acariciam a ternura.

Acolhem e transformam as provações,
Movimentam e dançam novas canções,
Animam e compartilham belas intenções,
Reacendem e vivem novas motivações,
Abraçam e saboreiam inusitadas emoções,
Libertam e aquecem muitos corações.

A quem faz de sua vida
um presente para os outros.

A vocês que fizeram parte do meu caminhar
e me ensinaram a viver.

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"Sonhe com aquilo que você quiser,
seja o que você quiser ser,
porque você possui apenas uma vida
e nela só se tem uma chance de fazer aquilo que se quer.
Tenha felicidade bastante para fazê-la doce,
dificuldades para fazê-la forte,
tristeza para fazê-la humana
e esperança para fazê-la feliz.
As pessoas mais felizes não têm as melhores coisas.
Elas sabem o fazer das oportunidades
que aparecem em seus caminhos..."

Clarice Lispector

SUMÁRIO

Apresentação

Essa Tese de Doutorado segue as novas orientações propostas pelo Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul (FO/PUCRS), que visando publicação dos conhecimentos científicos produzidos na formação do aluno do curso de pós-graduação *strictu sensu* estabelece a defesa de tese na forma de artigos. Uma maneira inteligente e eficaz para aumentar o número de publicações e a pontuação do curso junto à Coordenação de Aprimoramento de Pessoal do Ensino Superior - CAPES. É uma proposta oportuna diante dos desafios que estamos vivendo, pois apresenta possibilidades para as necessidades de produção e divulgação do conhecimento científico, como também uma maneira para elevar a nota do curso.

Essa tese apresenta três artigos: o primeiro relacionado a estratégias no planejamento e na condução de estudos não aleatórios na Cirurgia e Traumatologia Bucomaxilofacial (CTBMF), esse artigo faz considerações sobre o tipo de pesquisa clínica adotada peculiarmente na área de CTBMF, considerando as dificuldades e limitações de se realizar estudos clínicos baseados em fortes evidências científicas nessa área; o segundo; uma revisão de literatura sobre o ameloblastoma enfocando os aspectos histopatológicos e as implicações clínicas na indicação dos tratamentos; e o terceiro é um estudo experimental em tíbias de ratos que avalia o reparo ósseo em cavidades submetidas ao contato com solução de Carnoy.

O primeiro estudo avalia os possíveis desenhos e estratégias para se conduzir um estudo clínico. No caso de tratamento de ameloblastomas o melhor desenho que

proporcionará uma evidencia científica válida são séries-de-casos prospectivos e ou estudos coorte. O segundo artigo faz uma revisão da literatura sobre os tipos anatomopatológicos de ameloblastomas com o objetivo de determinar uma relação entre as características histológicas e o comportamento biológico do tumor. E finalmente, no terceiro artigo, a solução de Carnoy é testada experimentalmente em cavidades ósseas e as alterações no reparo ósseo são avaliadas, essa solução tem sido utilizada para diminuir a taxa de recidiva do ameloblastoma unicístico, após a enucleação do tumor.

A Discussão geral faz referência às idéias sobre futuras pesquisas, e elucubrações de como, cientificamente, chegar à verdade sobre o melhor tratamento desse tumor.

No sentido de realização de um sonho, e cumprimento de um dever, este trabalho resume o esforço e dedicação empreendidos durante os anos do Curso de Doutorado em Odontologia na área de concentração de Cirurgia e Traumatologia Bucomaxilofacial da PUCRS, refletindo uma amostra do acúmulo e geração de conhecimentos adquiridos nesse período.

Nenhuma obra é perfeita, e não contamos que esta fuja à regra universal: esperamos, no entanto, que as críticas construtivas nos sejam enunciadas e não apenas murmuradas para que possamos, em eventuais revisões, atualizar as omissões ou erros porventura cometidos.

Esperamos que esse trabalho possa ser aproveitado pela sociedade, e que além dos frutos já colhidos, possa semear outras gerações de pesquisas sobre esse assunto.

Artigos

Estratégias no planejamento e condução de estudos não-aleatórios na Cirurgia e Traumatologia Bucomaxilofacial

Issues in the planning and conduct of non-randomised studies in Oral and Maxillofacial Surgery

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Resumo

Esse artigo aborda e discute tópicos relacionados ao planejamento e implementação de estudos clínicos não aleatórios nas pesquisas em Cirurgia e Traumatologia Bucomaxilofacial.

Uma série de casos bem conduzida é apropriada para demonstrar a segurança de uma intervenção cirúrgica. O desenho de uma série de casos envolve o estabelecimento de uma intervenção definida a um grupo de pacientes com o objetivo de descrever os resultados finais do tratamento, incluindo complicações do tratamento. Não há um procedimento alternativo que serve como controle. O aspecto chave consiste em assegurar o arrolamento de todos os pacientes elegíveis e obter uma amostra suficientemente ampla para permitir uma estimativa precisa e válida dos riscos de complicações. Complicações pós-operatórias devem ser claramente definidas e plenamente documentadas durante um período pré-definido de seguimento do paciente e a perda de seguimento deve ser minimizada.

Estudos comparativos são necessários para demonstrar a efetividade do tratamento. Se um estudo controlado aleatório não é viável, um desenho observacional como estudos coorte ou um estudo caso-controle devem ser considerados. Em um desenho observacional, a decisão do tratamento é feita pelo cirurgião. Em um estudo caso-controle, os pacientes são selecionados baseados nos resultados de seus tratamentos ou tipo de exposição, registrados retrospectivamente. Em um estudo coorte, grupos de pacientes são selecionados baseados em seus tratamentos e são seguidos pelos seus resultados. Existem inúmeras variações. Os dados podem ser coletados prospectivamente ou retrospectivamente; grupos de comparação podem ser concorrentes ou não concorrentes,

ou estudados em diferentes lugares. O desenho ideal é adaptado à questão clínica e a configuração da pesquisa, considerando a respectiva força metodológica e fragilidade das opções disponíveis. A força do estudo observacional é a sua proximidade da prática clínica diária. As limitações são as possibilidades de vários vieses e fatores de confusão. Apesar dos muitos desafios para a validade interna de estudos não-aleatórios em cirurgia bucomaxilofacial, é possível a utilização de tais desenhos para fornecer respostas razoavelmente válidas a questões clinicamente importantes.

Palavras chaves: Cirurgia Bucomaxilofacial; pesquisa clínica; desenho de estudos; estudos não-aleatórios; séries-de-casos; estudo coorte

Abstract

This paper discusses topics related to the planning and implementation of non-randomised clinical studies in oral and maxillofacial surgery.

A well-conducted case-series is appropriate to demonstrate the safety of a surgical intervention. The case-series design involves the provision of a defined intervention to a group of patients with the ultimate objective of describing the final outcome, including such occurrences as complications. There is no alternative procedure serving as a control. The key aspects are to ensure enrolment of all eligible patients and to obtain a sufficiently large sample size to allow precise and valid estimation of complication risks. Targeted complications should be clearly defined and fully documented during a pre-defined follow-up period. Loss to follow-up should be minimised.

Comparative studies are required to demonstrate treatment effectiveness. If a randomised controlled trial (RCT) is not feasible, an observational design such as a cohort or a case-control study should be considered. In observational designs, the treatment decision is made by the surgeons. In a case-control study, patients are selected based on their outcomes and their treatment or exposure status is recorded retrospectively. In a cohort study, groups of patients are selected based on their treatment and are followed for outcomes. There are numerous variations. Data can be collected prospectively or retrospectively; comparison groups may be concurrent or non-concurrent, or studied at different locations. The optimal design is tailored to clinical questions and research settings, while keeping in mind the respective methodological strengths and weaknesses of available options. The strength of the observational study is its proximity to daily clinical

practice. The limitations are the possibility of numerous biases and confounding factors. Despite many challenges to the internal validity of non-randomised studies in orthopaedics surgery, it is possible to use such designs in order to provide reasonably valid answers to clinically important questions.

Keywords: Oral and maxillofacial surgery; Clinical research; Study designs; Non-randomised studies; Case-series; Cohort study

Introdução

Há um crescente interesse na aplicação de abordagens baseadas em evidências na Cirurgia Bucomaxilofacial. A prática da Odontologia baseada em evidências é um processo pelo qual a decisão de tratamento é feita baseada na combinação da experiência clínica com a melhor evidência científica avaliada em estudos clínicos e, a preferência do paciente[1]. A evidência científica de uma pesquisa foi classificada em níveis de I a V, onde os estudos de nível I são os de maior força de evidência e os de nível V os de menor (Tabela 1)[2]. Autores[3] demonstraram que dos artigos publicados nas principais revistas da especialidade, 40% são de nível IV e 50% de nível V (sem evidência); 2% são de nível II e 8% de nível III, não encontraram nenhum artigo 0% de nível I. Esse estudo demonstrou que 90% dos artigos publicados nas principais revistas internacionais de cirurgia bucomaxilofacial tem baixo nível de evidência e consistem em séries-de-casos, relatos de casos, estudos animais, estudos laboratoriais, notas técnicas, artigos tutoriais e artigos de revisão. Isso reflete a peculiar dificuldade de desenvolver estudos aleatórios-controlados na área cirúrgica em geral. A maior dificuldade na realização desses estudos é a alocação aleatória dos pacientes, o tamanho da amostra e os custos também são outros fatores que dificultam e inviabilizam a execução desse desenho de estudo.

Quando um estudo aleatório-controlado não é praticável, os pesquisadores podem considerar como alternativa os desenhos de pesquisa não-aleatórios. A seguir descreveremos as chaves metodológicas relacionadas às estratégias para o planejamento e implementação de estudos clínicos não-aleatórios e as ameaças para a validade de seus resultados.

Tabela 1 – Níveis de evidência para questões primárias de pesquisa

	Tipos de estudo			
	Estudos terapêuticos – que investigam os resultados de tratamentos	Estudos prognósticos – investigam os resultados da doença	Estudos diagnósticos – investigam os testes diagnósticos	Análise de decisão e econômica – desenvolvem um modelo de decisão ou modelo econômico
Nível I	1. Estudos aleatórios (a) diferença estatisticamente significante (b) diferença não estatisticamente significante mas próxima ao intervalo de confiança 2. Revisão sistemática[b] de estudos aleatórios de nível I (e os estudos são homogêneos)	1. Estudos prospectivos[a] 2. Revisões sistemáticas[b] de estudos nível I	Teste de critérios diagnósticos anteriormente desenvolvidos em pacientes consecutivos (com uma referência aplicada como "padrão ouro") 2. Revisões sistemáticas[b] de estudos nível I	1. Sensibilidade clínica dos custos e alternativas; valores obtidos de muitos estudos; com análise de sensibilidade multifatorial 2. Revisões sistemáticas[b] de estudos nível I
Nível II	1. Estudos coorte prospectivos[c] 2. Pobre qualidade de Estudos aleatórios controlados (ex <80% seguimento) 3. Revisão sistemática (a) estudos nível II (b) estudos nível I não-homogêneos	1. Estudos retrospectivos[d] 2. Controle não –tratados de um estudo aleatório controlado 3. Revisão sistemática[b] de estudos nível II	1. Desenvolvimento de critério de diagnóstico em pacientes consecutivos (com uma referência "padrão ouro") 2. Revisão sistemática[b] de estudos nível II	1.Sensibilidade clínica de custos e alternativas; valores obtidos de estudos limitados; com análise de sensibilidade multifatorial 2. Revisão sistemática[b] de estudos nível II
Nível III	1. Estudos caso-controle[e] 2. Estudos coorte retrospectivos 3. Revisão sistemática de estudos nível III		1. Estudos de pacientes não-consecutivos; sem um "padrão ouro" aplicado 2. Revisão sistemática de estudos nível III	1. Análise baseada em alternativas limitadas e custos; e pobre estimativa 2. Revisão sistemática de estudos nível III
Nível IV	Série de casos (grupo controle histórico ou ausente)	Série de casos	1. Estudo caso-controle 2. Pobre padrão de referência	Estudos sem análise de sensitividade
Nível V	Opinião de especialista	Opinião de especialista	Opinião de especialista	Opinião de especialista

[a] Todos os pacientes foram inscritos no mesmo ponto de suas doenças (exceto coorte) com ≥ 80% de seguimento dos pacientes inscritos
[b] A combinação de resultados de dois ou mais estudos prévios
[c] Pacientes comparados com grupo controle, no mesmo tempo dos pacientes tratados na mesma instituição
[d] Pacientes com um resultado particular "caso" diferente do grupo

Bhandari M, Swiontkowski M, Einhorn T, et al. Inter-observer agreement in the application of the levels of evidence to scientific papers in the Journal Bone and Joint Surgery. J Bone Joint urg Am 2004;86:1717-20.

Desenho dos estudos

Um esquema dos principais estudos clínicos de intervenções cirúrgicas é apresentado na Figura 1. Nesse texto usaremos o termo “investigação” em sentido amplo sem apontar um desenho de estudo em particular.

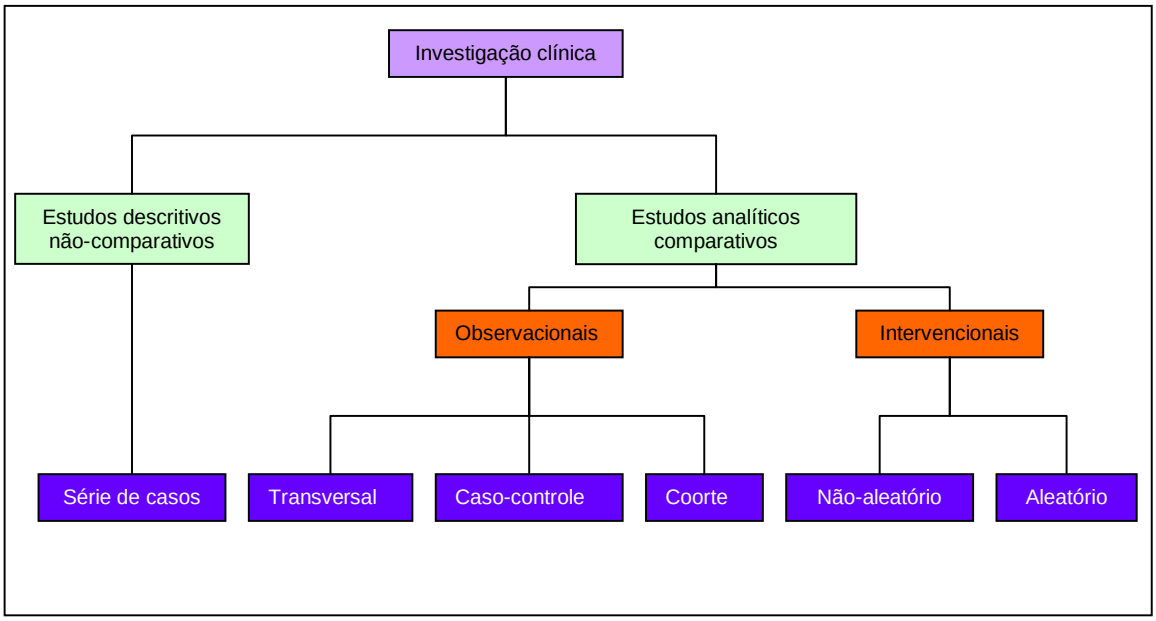

Figura 1 - Classificação dos desenhos de estudos mais utilizados.

Na definição de desenhos adequados de investigações, o primeiro passo é definir se a intervenção de interesse está sendo comparada com uma ou mais intervenções. Se não há grupo de comparação envolvido, o estudo é “investigação não-comparativa”. Investigações não comparativas também são referidas como “estudos descritivos” porque seu principal propósito é descrever experiências com abordagens de tratamentos novos ou complexos. Eles são usados para documentar a segurança da intervenção e seus resultados são usados para gerar hipóteses sobre a efetividade do tratamento. Estudos descritivos ligam o desenvolvimento de abordagens (terapias ou técnicas) às pesquisas clínicas e, mais

tarde, às práticas clínicas. O desenho clínico mais comum de estudos descritivos é a "série-de-casos". Uma série-de-casos descreve casos clínicos comuns. Outros termos podem ser encontrados como teste de manipulação, documentação de séries. Por exemplo: baseado em uma série de casos foram[4] avaliados a estabilidade pós-cirúrgica da osteotomia Le Fort I com fixação interna anterior, sem fixação posterior no pilar zigomaticomaxilar e os resultados foram documentados prospectivamente imediatamente após a cirurgia nos tempos de 42,1 dias e 14,8 meses em média. A série de casos deve ser distinguida dos "relatos de caso" que geralmente descrevem um caso incomum, extremo, desordens ou complicações raras e incluem um número limitado de pacientes (geralmente menos que 10).

Investigações comparativas são chamadas "estudos analíticos" porque seu principal objetivo é fazer inferências sobre a efetividade de duas ou mais intervenções. Eles são usados geralmente para testar hipóteses específicas de pesquisa. Se as intervenções são claramente definidas e padronizadas, então a investigação é mais experimental na natureza e o termo "ensaio" *(trial)* é usado. Ensaios aleatórios geralmente comparam intervenções bem definidas e controladas e são denominados "ensaios aleatórios controlados" *(Randomized Controlled Trials)*. O grau que a intervenção cirúrgica é controlada varia entre os ensaios. A terminologia "estudos experimentais" *(experimental study)* é geralmente usada para ensaios controlados para ressaltar sua similaridade com experimentos de laboratório. Na maioria dos casos, entretanto as intervenções cirúrgicas já não estão mais em fase experimental quando há avaliação em um "ensaio controlado". Em ensaios controlados não-aleatórios o desenho assemelha-se ao do ensaio clínico aleatório controlado em todos os aspectos, exceto pela alocação aleatória do grupo de tratamento.

Investigações em cirurgia bucomaxilofacial geralmente usam dados que são obtidos de prontuários ou são coletados prospectivamente sem intervir na decisão do processo de tratamento. Nesses estudos, o tipo de tratamento é decidido de acordo com o padrão de abordagem clínica, (que é a interação entre o paciente, o dentista e outros fatores) e não pelo protocolo do estudo, os pesquisadores do estudo não têm controle sobre a intervenção e apenas observam o que os cirurgiões estão fazendo. Tais desenhos de estudo são chamados "estudos observacionais". A vantagem dessa abordagem é que os resultados do estudo são o mais perto daqueles obtidos na prática clínica diária. Ao mesmo tempo esses estudos são significativamente limitados na extensão das conclusões válidas que podem alcançar sobre a efetividade do tratamento. Dois principais desenhos de estudos observacionais são: estudo coorte e estudo caso-controle.

Estudos coorte (sinônimos com estudos de incidência, estudos longitudinais, estudos de seguimento *follow-up*) acompanham grupos de pacientes por um determinado tempo em seqüência para observar e comparar a ocorrência/incidência ou medir resultados específicos. O desenho de coorte mais comum é a comparação de dois grupos concorrentes de tratamentos para uma mesma situação clínica. Há, entretanto, muitas variáveis que podem influenciar consideravelmente nas questões clínicas: disponibilidade dos dados, questões éticas e logísticas. Informações sobre os pacientes, exposições a tratamentos e resultados podem ser coletados prospectiva ou retrospectivamente. O último é baseado em uma revisão retrospectiva dos dados históricos dos prontuários e outras origens de informações. Por exemplo, num estudo coorte restrospectivo[5] foi avaliada as características de caninos mandibulares que sofreram transmigração, num outro estudo retrospectivo[6] os resultados do tratamento não cirúrgico de fraturas condilares foram

avaliados. A análise pode ser comparativa entre dois grupos de tratamento que podem ser concorrentes, quando ambos os grupos forem tratados no mesmo período ou não concorrentes, quando são tratados em períodos diferentes. Quando os cirurgiões estão convictos sobre o benefício do novo tratamento, pode ser difícil obter um grupo controle concorrente. Em tais casos dados históricos podem ser obtidos para o grupo controle. Finalmente, grupos de estudos podem também serem documentados por diferentes cirurgiões em diferentes clínicas. Um grupo de cirurgiões ou clínicas pode aplicar um tipo de tratamento e o outro grupo aplica a intervenção controle. Entretanto, estudando grupos em diferentes lugares e em diferentes tempos o estudo se torna mais fraco, pois os resultados podem ser atribuídos ao tempo, fatores relacionados à clínica e ao cirurgião além das intervenções sobre a investigação. A força do estudo de coorte depende, sobretudo, da disposição de uma comparação direta de dois tratamentos em grupos similares. Finalmente, comparando resultados de uma intervenção com as que foram previamente publicadas na literatura (isso é algumas vezes referida como “controle da literatura”) é uma comparação de validade limitada.

A maior limitação dos estudos coorte é que o grupo de pacientes sendo comparado pode diferir nas características básicas importantes para o resultado. Essas características, que podem influenciar os resultados são referidas como confundidores. Isso pode resultar em uma situação onde diferentes resultados são atribuídos ao efeito do tratamento, quando tais diferenças são na verdade os resultados de outro fator (confundidor). Para reduzir o impacto dos confundidores os pesquisadores devem obter informações sobre as variáveis confundidoras e usar vários desenhos e abordagens estatísticas para ajustar seus resultados minimizando os efeitos de confusão. Estudos coorte e ensaios controlados não aleatórios

têm desenhos similares e diferem principalmente na consideração para a extensão do controle dos estudos de intervenção. O termo “estudo coorte” é frequentemente usado para descrever um ou outro.

Estudos caso-controle comparam pacientes com alguns resultados definidos com um grupo controle de pacientes sem tais resultados. Informações sobre exposição (ex. tratamento) são então coletadas retrospectivamente. Estudos caso-controle podem ser usados para investigar resultados raros bem como avaliar falhas no tratamento ou ocorrência de complicações raras, eles são incomuns na investigação da efetividade do tratamento. São mais usados para investigar fatores de risco para ocorrência de complicações. Num estudo caso-controle[7]que investigou osteoartrose após fratura de côndilo a gravidade da fratura do côndilo foi determinante no desenvolvimento dessa complicação. Estudos caso-controle são de curta duração por sua natureza retrospectiva. Entretanto, Eles são sujeitos para diferentes tipos de viés, em particular aqueles relacionados à escolha do grupo controle e à limitação da coleta de dados retrospectivos.

Série-de-casos é apropriada para documentar a segurança da intervenção

O principal objetivo da “série-de-casos” é demonstrar a segurança de um determinado tratamento. O estudo deve demonstrar que complicações sérias e eventos adversos não ocorrem, ou ocorrem com uma baixa e aceitável freqüência. A segurança pode ser detectada sem recorrer a um grupo controle, uma série-de-casos bem conduzida é aquela em que o pesquisador assegurou que a aleatoriedade e a origem sistemática de erro

são limitadas e que os resultados consistem em uma representação válida da população alvo. Os passos importantes para condução de uma série-de-casos são as seguintes:

Especificar a questão clínica no objetivo do estudo

Todos os estudos clínicos devem estipular objetivos. Para a série-de-casos, a questão clínica a ser respondida deve incluir a população alvo definida por critérios de inclusão e critérios de exclusão, o tratamento que deve ser aplicado, e os resultados a serem avaliados. Por exemplo, pacientes adultos com fraturas de côndilo tratados de maneira conservadora para determinar as complicações de tratamento.

Integridade dos documentos de inclusão dos pacientes

Um dos mais importantes aspectos metodológicos para a série-de-casos é a validade externa. O pesquisador deve assegurar que os resultados de uma série-de-casos aplicam-se a população alvo definida pelos critérios de inclusão e exclusão e que nenhum paciente elegível seja ignorado. A integridade de inclusão de pacientes dentro do estudo pode ser melhorada pelo arrolamento de casos prospectivos o que é mais confiável que somente revisar os casos retrospectivos. Sempre que possível, medidas devem ser adotadas a cada local do estudo e a lista de pacientes checada e identificar todos os pacientes potencialmente elegíveis. Isso geralmente é alcançado por um estudo com o pessoal no local como, por exemplo, um estudo com as enfermeiras. A documentação sistemática prospectiva de todos os pacientes elegíveis incluindo um mínimo de informações anônimas deve ser usada em todos os estudos série-de-casos prospectivos. Essas informações reservam exploração de diferenças entre os pacientes que receberam a

intervenção estudada e aqueles que não, bem como explorar as diferenças entre os pacientes participantes e não participantes.

Em uma abordagem controlada, todos os pacientes definidos por critério de inclusão devem receber a intervenção alvo. Em uma abordagem observacional, entretanto, os cirurgiões escolhem a alternativa de tratamento. Em cada situação a verdadeira população alvo é definida por indicações específicas para receber a intervenção em estudo, esses fatores de indicação devem ser objetivamente definidos e registrados, pois pode haver diferenças entre as intervenções, clínicas e cirurgiões.

Tamanho da amostra

Para se afirmar verdades válidas para determinadas população não é necessário estudar todos os indivíduos dessa população, o que seria inviável. Felizmente para se chegar a uma validade razoável do estudo uma estimativa precisa dos valores populacionais pode ser derivada de amostras representativa dos pacientes. As amostras têm de ser de tamanho suficiente para limitar o efeito de variações aleatórias na precisão da estimativa. Para estimar a necessidade do tamanho da amostra o pesquisador deve ter uma idéia sobre a freqüência dos resultados e o nível de precisão desejado.

O tamanho da amostra depende do erro aleatório inerente a qualquer investigação amostral. Amostras grandes, erros pequenos; amostras pequenas erros grandes. Outro fator que influi decisivamente no tamanho da amostra é a magnitude do efeito, ou seja, quanto maior for a diferença entre o que se compara menor será a amostra, e quanto menor for essa diferença maior será a amostra.[8]

A amostra confiável deve refletir a população alvo, e o tamanho dessa amostra deve ser tal que limite os erros de aleatoriedade para que se chegue a conclusões válidas. Há diversas maneiras de se calcular o número ideal de pacientes de uma amostra para se chegar a conclusões válidas. Algumas variáveis do estudo devem ser consideradas nessa estimativa.

Todas as complicações e eventos adversos devem ser documentados

Os resultados a serem avaliados devem ser claramente definidos de modo que não haja ambigüidade na definição dos casos nos quais os resultados ocorrerem. O protocolo do estudo deve listar as complicações esperadas, distinguidas como intra e pós-operatórias. Algumas complicações são bem conhecidas e definidas (ex: infecção de ferida, definida por critérios como do centro de prevenção e controle de doenças), mas outros tipos de complicações geralmente permanecem mal definidas (ex: não há definição uniforme do atraso no reparo e da não união de fraturas), os pesquisadores devem sustentar e justificar a definição usada em seu estudo.

O tempo que ocorre a complicação também é importante, e o protocolo do estudo deve especificar o tempo de acompanhamento pós-operatório dos pacientes. Por exemplo, a diferença entre uma janela de 6 e 12 meses pode não ter significado na validade do risco estimado para a ocorrência de uma complicação esperada nos primeiros 3 a 4 meses. Entretanto, o tempo de seguimento maior pode ter um impacto na validade da estimação de ocorrência de complicações tardias.

Séries-de-casos são retrospectivas quando os dados sobre os pacientes e resultados já foram coletados quando o estudo se inicia, bem como quando eles são baseados em

revisões de registros médicos. Eles são prospectivos quando os pacientes são acompanhados depois de iniciar o estudo para coletar dados necessários. Série-de-casos prospectivos bem documentados tem vantagens sobre as retrospectivas, pois dão a possibilidade de um controle ativo do pesquisador sobre a integridade dos eventos de registro e documentação, algo que é impossível em uma abordagem retrospectiva.

Análise de dados e registro dos resultados

Complicações de tratamento geralmente são relatadas por tabulação e classificação de acordo com seus níveis de gravidade (“médio”, “moderado”, “grave”) e na sua relação com o tratamento (“definitivo”, “provável”, “possível”, “não-relatado”). A ocorrência de uma complicação grave relacionada a um tratamento definitivo pode indicar a interrupção do estudo. Para eventos menos graves, o número de complicações observadas (geralmente nos casos de ausência) tem um valor limitado sem considerações cuidadosas do número de pacientes “de risco” em qualquer tempo específico do tratamento.

O termo mais usado “taxa de complicação” é o número cumulativo de complicações num determinado tempo. Considerando que não se perca nenhum paciente durante o seguimento, os riscos de complicações são simplesmente calculados como o número de complicações relativas ao número de pacientes tratados. Por exemplo, um trabalho[9] avaliou as complicações cirúrgicas após tratamento aberto para fraturas do côndilo mandibular. Um total de 178 pacientes com fraturas unilaterais do côndilo mandibular foi incluído nesse estudo; 85 receberam o tratamento fechado e 93 o tratamento aberto. Os pacientes foram avaliados até 3 anos após o tratamento. Houve poucas complicações intra ou pós-operatórias. Com 6 semanas 17,2% dos pacientes tratados por redução aberta tinham algum problema no nervo facial que foi resolvido após 6 meses; 7,5%

apresentaram cicatriz. O tempo de seguimento do paciente, importante nesse estudo prospectivo, variou desde o momento da cirurgia até 3 anos após. Complicações como infecção e hemorragias são registradas nos períodos iniciais do estudo. Para complicações tardias o período de seguimento é critico, enquanto que a avaliação da remodelação do côndilo um curto período de seguimento é insuficiente. A perda de seguimento dos pacientes nesse tipo de estudo pode ser alta e há necessidade de ajustes. É importante registrar o tempo de seguimento para cada paciente bem como o tempo de ocorrência da complicação do tratamento. Se o período de observação é conhecido para cada paciente, incluindo aqueles que perderam o seguimento e se o tamanho da amostra é suficientemente grande, é possível aplicar métodos estatísticos mais avançados e derivar estimativas mais corretas do risco de complicações de tratamento.

Outros propósitos da série de casos

Geralmente o objetivo da investigação é testar uma hipótese do que é “melhor” ou “pior” para o paciente com o tratamento investigado. O estabelecimento dessas hipóteses implica numa comparação com um tratamento controle, idealmente no desenho de estudos clínicos aleatórios controlados. Quando o estudo aleatório controlado não é viável, desenhos comparativos não-aleatórios devem ser considerados. Veremos a seguir os principais ensaios metodológicos principais de desenhos não-aleatórios com foco específico no estudo de coorte. Estudos coorte são mais expostos a viés que estudos aleatórios controlados. Os pesquisadores devem estar cientes desse potencial de viés e estar certos que eles podem limitar a validade dos resultados[10]. O principal passo para desenhos comparativos não-aleatórios são descritos abaixo.

Especificidade da questão clínica no objetivo do estudo

A formulação de questões clínicas para estudos coorte é similar àquelas para ensaios aleatórios controlados. A questão deve incluir a população alvo definida pelos critérios de inclusão e exclusão, a intervenção a ser aplicada, a intervenção sobre comparação, e os resultados a serem avaliados. Por exemplo, pacientes adultos com uma fratura isolada de côndilo tratada com fixação interna podem ser comparados a pacientes similares tratados de maneira conservadora com fisioterapia, tendo como critério de avaliação de resultados parâmetros funcionais avaliados em tempos tardios.

O registro dos pacientes deve ser representativo da população alvo

Um estudo clínico deve ser representativo da população que a conclusão irá generalizar, tanto para série-de-casos como também para os estudos comparativos. Uma diferença sistemática na característica entre os pacientes que são selecionados para o estudo e aqueles que não foram podem indicar uma forma de viés de seleção. Isso afeta a validade externa, mas um estudo sem uma amostra não representativa pode ainda ter boa validade interna e apresentar conclusões válidas sobre a efetividade do tratamento. Pacientes incluídos em estudos aleatórios controlados (elegíveis e participantes) tendem a ter um prognóstico diferente dos pacientes identificados de base de dados clínicos. A participação dos pacientes em estudos prospectivos não-aleatórios, entretanto, pode estar limitada devido à necessidade de se obter consentimento informado dos pacientes. Por exemplo, imagine que os participantes do estudo são mais jovens que os não participantes; se a idade influenciar na efetividade do tratamento, os resultados podem estar enviesados e não

totalmente aplicados na população alvo de pacientes. Apesar disso os pesquisadores são encorajados a manter uma “lista clínica” de pacientes elegíveis para se entender as razões para não participação em estudos cirúrgicos comparativos. Isso pode ajudar a descrever melhor a validade externa do estudo e também desenvolver estratégias para melhorar o recrutamento de pacientes. A taxa de participação de pacientes elegíveis deve ser considerada em estudos prospectivos assim como um período de arrolamento é determinado em um plano de estudo.

Diferenças nos fatores prognósticos devem ser registradas

Viés de alocação ocorre quando a alocação de pacientes para grupos de intervenção está relacionada a fatores prognósticos para os resultados do estudo. Viés de alocação é uma forma de viés de seleção, a situação na qual o tratamento aparentemente é efetivo devido à maneira que os pacientes são selecionados nos grupos ao invés do verdadeiro efeito do tratamento. Esse viés ocorre em estudos controlados aleatórios quando o processo da seqüência de aleatoriedade não passa por cegamento antes da inclusão dos pacientes. Em um estudo não-aleatório, alocação do tratamento não é escondida, mas decidida pelo cirurgião, e os resultados prováveis resultam em um grupo desequilibrado em consideração aos fatores de base e prognósticos por causa da sua influência sobre a escolha do tratamento. Conseqüentemente, estudos não-aleatórios são sujeitos a viés de seleção. Em estudos observacionais, os fatores associados com a escolha do tratamento podem ser pouco ou numerosos, objetivos ou subjetivos, consistentes ou inconsistentes, mas os pesquisadores devem estar atentos para documentar eles e entender o processo de decisão. Devendo um ou vários desses fatores forem prognósticos para os resultados do estudo, os diferentes resultados observados entre os grupos irão ser confundidos.

Conseqüentemente, no plano de estudo, os pesquisadores devem desenvolver uma lista de fatores prognósticos relevantes após profunda revisão de literatura e discussão com clínicos experientes, incluindo esses envolvidos no estudo. A informação sobre essas características prognósticas devem ser registradas antes e após os exames para ajustar os achados para o efeito de confundimento.

A intervenção desejada deve ser distinguida de mudanças de tratamento não planejadas

Nos estudos controlados aleatórios (randomizados), a aplicação dos princípios de intenção de tratar implica que os pacientes sejam analisados no grupo que eles foram alocados. Esse conceito é facilmente entendido no contexto de um estudo controlado aleatório, pois os tratamentos “pretendidos” são definidos no protocolo da pesquisa pela alocação aleatória. Em estudos não-aleatórios, a “intenção” de tratar é mais difícil de definir. Planejamento dos tratamentos, por exemplo: o tipo de material de osteossíntese empregado, a abordagem cirúrgica, deve ser considerado como “intenção” de tratamento. O plano de tratamento (não somente o tratamento inicial) que é determinado depois do diagnostico deve ser documentado. Qualquer mudança nesse plano causado por circunstâncias infortuitas, tais como problemas técnicos durante a cirurgia, falha na redução da fratura ou ocorrência de complicação, devem ser registrados como “não-intencional”. Isso é comum em estudos de intervenções cirúrgicas. Quando conduzidos a análise de acordo para os princípios de intenção de tratar, grupos de tratamento devem ser formados com base nos tratamentos planejados e não nos realmente executados. Mas geralmente grupos não-aleatórios são formados pelo pesquisador baseados no tratamento que efetivamente recebeu sendo ele planejado ou não, esse tipo de análise é baseada em

como o paciente foi tratado. É o que acontece nos estudos retrospectivos observacionais que têm apenas dados históricos documentados somente do tratamento que os pacientes receberam, pois falta a informação do que estava planejado para o tratamento.

Todos os pacientes e grupos de tratamento devem ser seguidos similarmente e examinados em tempos chaves clinicamente relevantes e definidos.

Viés de registro ocorre quando o registro dos resultados não é padronizado entre os pacientes e os grupos de intervenção. Viés de registro faz parte do grande grupo de viés de informação. Por exemplo: se o grupo controle é examinado antes (5 meses) que o grupo de intervenção (6 meses), é esperado que o padrão de cura ou resultados funcionais irão erroneamente favorecer o grupo da intervenção. Estudos prospectivos geralmente não sofrem viés de registro, entretanto, viéses de registro estão presentes em estudos retrospectivos. Em cada situação, é recomendável que os pesquisadores definam um aceitável “tempo de seguimento” para cada resultado e analisem os dados de acordo. Em estudos prospectivos, um desvio tolerável no tempo de seguimento pré-determinado deve ser selecionado e monitorado.

Viés de perda do seguimento ocorre quando os pacientes são perdidos durante o seguimento por razões que são diretamente ou indiretamente ligadas a intervenção recebida e é um dos resultados do ensaio. Um exemplo é o paciente que se cura de uma fratura pode não sentir a necessidade de voltar para exame final. Isso é importante tópico para todas as investigações clínicas, incluindo estudos controlados e aleatórios. Esforços devem ser feitos para minimizar a ”perda de seguimento”. O protocolo de estudo deve descrever os passos tomados para limitar o risco de perda de pacientes, e o estudo deve

documentar as razões para perda do pacientes. A extensão de perda de seguimento do paciente pode causar erros na interpretação dos resultados e devem ser considerados em cada estudo.

Desequilíbrios entre os grupos de tratamento nas características básicas devem ser controlados para a análise de dados

Viés de confundimento ocorre quando grupos de intervenção diferem em um fator prognóstico que não está sendo levado em consideração na análise. Um fator prognóstico para os resultados do estudo é o fator de confundimento somente se isso diferir entre os grupos de tratamento. Em estudos controlados aleatórios, as diferenças básicas ocorrem devido à natureza do estudo. Estudos não-aleatórios devem controlar os fatores de confundimento e aplicar métodos estatísticos avançados apropriados em ordem para ajustar as diferenças nos fatores prognósticos de linha de base. Entretanto, é importante ter em mente que nem todas as diferenças podem ser adequadamente ajustadas devido à falta de dados ou limitações nos métodos estatísticos. Por essa razão, confundimento residual sempre permanece uma explicação alternativa para esses efeitos vistos em um estudo observacional. Essa é uma limitação dos estudos observacionais que eles não possibilitam superar satisfatoriamente e, além disso, irá sempre ser menos confiável nos achados de estudos observacionais comparados com aqueles provenientes de estudos aleatórios controlados bem conduzidos.

Considerações finais

Descrevemos algumas estratégias importantes no planejamento e execução de estudos não-aleatórios em cirurgia bucomaxilofacial. A seleção de desenhos de estudos corretos depende do tipo de questão clínica e outros fatores como: a freqüência esperada dos resultados, volumes de pacientes, e disposição do paciente participar da pesquisa, etc. Os métodos de pesquisas clínicas atuais são aplicados para assegurar a validade dos resultados ambos externamente (em relação ao mais amplo da população de pacientes) e internamente (em relação a validade entre os grupos de comparação). Existem muitas outras importantes matérias no desenho e execução de uma pesquisa clínica[11] que não foram abordadas nesse texto. Encorajamos os leitores a consultar literatura adicional do tópico. Além dos tópicos considerados nesse texto, é sempre recomendável discutir o protocolo de estudo com colegas e profissionais metodologistas. Somente com cuidadoso esforço pode se alcançar o melhor desenho possível para encontrar uma questão específica de pesquisa e configuração. Pesquisadores não devem ser desencorajados se o desenho de estudo ideal não é factível, mas fazer o melhor compromisso metodológico e avaliar como esses compromissos podem influenciar a validade dos resultados.

Referências

1. Goldstein GR. What is evidence based dentistry? Dent Clin North Am 2002;46(1):1-9.

2. Bhandari M, Swiontkowski M, Einhorn T, et al. Inter-observer agreement in the application of the levels of evidence to scientific papers in the Journal of Bone and Joint Surgery. J Bone Joint Surg Am 2004;86:1717—20.

3. Lau SJ, Samman N. Levels of evidence and journal impact factor in oral and maxillofacial surgery. Int J Oral Maxillofac Surg 2007;36:1-5.

4. Yoon HJ, Rebellato J, Keller EE. Stability of the Le Fort I osteotomy with anterior internal fixation alone: a case series. J Oral Maxillofac Surg. 2005 May;63(5):629-34.

5. Buyukkurt MC, Aras MH, Caglaroglu M, Gungormus M. Transmigrant mandibular canines. J Oral Maxillofac Surg. 2007 Oct;65(10):2025-9.

6. Smets LMH, Van Damme PA, Stoeling PJW. Non-surgical treatment of condylar fractures in adults: a retrospective analysis. J Cramio Maxillofac Surg 2003;31:162-167.

7. Wu XG, Hong M, Sun KH. Severe Osteoarthrosis after fracture of the mandibular condyle: a clinical and histologic study of seven patients. J Oral Maxillofac Surg 1994;52:1138-142.

8. Luiz RR, Magnaninni MMF. O tamanho amostral na pesquisa odontológica. Ver Brasileira de Odontol e Saúde coletiva 2001;2(1):55-65.

9. Ellis III E, McFadden D, Simon P, Throckmorton G. Surgical complications with open treatment of mandibular condylar process fractures. J Oral Maxillofac Surg 2000;58:950-958.

10. Audige´ L, Hanson B, Bhandari M, Schemitsch E. Interpretation of data and analysis of surgical trials. Techn Orthop 2004;19:1—8.

11. Hulley SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB. Delineando a Pesquisa Clínica. Uma abordagem epidemiológica. 2006. Artmed. Porto Alegre. 2 edição. 374p.

Ameloblastoma – Types, subtypes and implications in management

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Abstract

In the treatment of ameloblastoma is essential to distinguish among the three clinical types: 1) intraosseous solid or multicystic ameloblastoma, 2) unicystic ameloblastoma, 3) peripheral (extraosseous) ameloblastoma - because they require different forms of treatment. Unicystic ameloblastoma is subdivided into three types with prognostic and therapeutic implications. The treatment methods for the ameloblastoma are still controversy. Enucleation and curettage are mostly chosen. Some clinicians used marsupialization to reduce the size of the lesion, followed by second stage surgery. These treatments can be followed by adjunctive therapy, including cryotherapy, chemical cauterization, peripheral ostectomy. The radical approach includes segmental resection, marginal resection, compost resection, total resection. This article shows the treatments of ameloblastoma and the pathologic considerations.

Key words: ameloblastoma; radical treatment; conservative treatment

Introduction

Ameloblastomas, previously called adamantinoma, are tumours of odontogenic origin with a high propensity for local recurrence. According to the WHO 1992 definition[1], ameloblastoma is a benign but locally invasive polymorphic neoplasm consisting of proliferating odontogenic epithelium, which usually has a follicular or plexiform pattern, lying in a fibrous stroma.

The classification of ameloblastoma in the past was poorly defined. Until the study by Eversole et al., 1984[2] ameloblastomas were classified according to histologic findings into follicular, plexiform, acanthomatous, granular cell, basal cell, squamous metaplastic, and other rare types. In recent years, the literature has divided clinical ameloblastomas into unicystic, multicystic or solid, peripheral, and malignant subtypes. This classification has a direct bearing on the pathologic behavior of these variants.

Multicystic and unicystic subgroups represent 86% and 13% of all ameloblastomas, respectively (Waldron, 2002[3] , Sapp et al., 2004[4]). Peripheral ameloblastoma is a rarer subgroup, representing 1% of all ameloblastomas (Philipsen et al., 2001)[5]. Malignant (metastasizing) ameloblastoma is extremely rare; an occurrence of 2% of all benign ameloblastomas has been reported, but this is probably too high a percentage (Houston et al., 1993)[6].

To enhance clarity in understanding the surgical management of ameloblastoma, it is important to first establish standardized definitions for three benign tumor types: peripheral, unicystic, and multicystic or solid.

Classification of the ameloblastoma

Solid or Multicystic Ameloblastoma

This variant of the ameloblastoma is encountered in patients over a wide age range (Ueno et al., 1986)[7]. It is rare in children in their first decade of life and relatively uncommon in the second decade (Takahashi et al., 1998)[8]. The tumor shows a relatively equal rate of occurrence in the third through seventh decades. There is no gender predilection, and racial predilection is most controversial. About 85% of this variant of the ameloblastoma occur in the mandible, most commonly in the molar/ramus region (Stoelinga and Bronkhorst, 1987).[45] About 15% of multicystic ameloblastomas occur in the maxilla, usually in the posterior regions (Nastri et al., 1995[9]; Jackson et al., 1996[10]; Sehdev et al., 1974[11]; Komisar, 1984[12]). A painless expansion of the jaws is the most common clinical presentation; neurosensory changes are uncommon, even with large tumors. The most common radiographic feature is that of a multilocular radiolucency. Buccal and lingual cortical expansion is common, frequently to the point of perforation. Resorption of adjacent tooth roots is common (Waldron, 2002[3]).

Ameloblastomas consist of epithelial strands or islands. The former pattern is called plexiform, the latter follicular (Barners, et al., 2005)[13]. Peripheral cells are columnar, while cells lying more centrally are fusiform to polyhedral and are loosely connected to each other. In the follicular type, in particular, an increase in intercellular edema may cause cysts that coalesce to form large cavities. In the plexiform type, cavity formation arises through stromal degeneration. The tumour infiltrates the adjacent cancellous bone, whereas cortical bone and periosteum usually expand but will not be perforated (Müller and Slootweg, 1985)[14]. Spread

into soft tissues is highly unusual. Acanthomatous, granular cell and basal cell (basaloid) ameloblastoma are variants with squamous metaplasia, granular cells and basaloid cells, respectively. Ghost cells are rarely seen. Desmoplastic ameloblastoma shows a dense collagenous stroma with dispersed strands of epithelium, sometimes with a peripheral rim of dark-staining cuboidal cells and a compact centre with whorling spindle-shaped epithelial cells. Within the stromal component, active bone formation can be observed (Philipsen, Reichart and Takata, 2001)[15].

Unicystic Ameloblastoma

Unicystic ameloblastoma refers to a pattern of epithelial proliferation that has been described in dentigerous cysts of the jaws that does not exhibit the histologic criteria for ameloblastoma. Vickers and Gorlin (1970)[16] published their findings regarding the histologic alterations associated with neoplastic transformation of ameloblastomatous epithelium. These histologic changes were (1) hyperchromatism of basal cell nuclei of the epithelium lining the cystic cavities, (2) palisading and polarization of basal cell nuclei of the epithelium lining the cystic cavities, and (3) cytoplasmic vacuolization, particularly of basal cells of cystic linings. They referred to these changes as early histopathologic features of neoplasia.

Unicystic ameloblastoma represents a cyst that is lined by ameloblastomatous epithelium. This epithelium may grow exophytically in the cyst lumen forming intraluminal nodules, or it may invade the fibrous cyst wall. Sometimes, the cyst lining itself lacks any features indicative of ameloblastoma, these being confined to intramural epithelial nests. Inflammatory alterations may obscure the specific histological details. This entity deserves separate consideration based on its clinical, radiographic, and pathologic features. This variant of ameloblastoma was reported to have shown less aggressive behavior than the conventional ameloblastoma (Robinson and Martines, 1977)[17]. Moreover, in many cases it may be treated more conservatively than the solid or multicystic ameloblastoma with the same degree of cure (Gardner and Corio, 1984)[18]. Unicystic ameloblastomas are most commonly seen in young patients, with about 50% of these tumors being diagnosed during the second decade of life. The average age of patients with unicystic ameloblastomas has been reported as 22.1 years, compared with 40.2 years for the solid or multicystic variant (Reichart et al., 1995)[19]. More than 90% of these tumors are found in the mandible, usually in the molar/ramus region (Gardner et al., 1987)[20].

Unicystic tumors include the tumors that have been referred to as mural ameloblastoma, luminal ameloblastoma, and ameloblastomas arising in dentigerous cysts (Robinson e Martinez, 1977[17]; Gardner, 1984[21]). Most unicystic ameloblastomas resemble dentigerous cysts clinically and radiologically.

VICKERS and GORLIN in 1970[16] described three distinct histopathological features for unicystic ameloblastoma and these were slightly modified by LEIDER et al. in 1985[22]. ACKERMAN et al. in 1988[23] reported a series of 57 unicystic

ameloblastomas and studied their histological features in detail. They modified the diagnostic criteria defined by ROBINSON and MARTINEZ 1977[17] and reclassified the unicystic ameloblastoma into three subtypes with prognostic and therapeutic significance.

Type 1 – In the *luminal unicystic ameloblastoma*, consisted of unilocular cystic lesions lined by epithelium exhibiting features of ameloblastoma (criteria defined by VICKERS and GORLIN[16]).

Type 2 – The *intraluminal unicystic ameloblastoma* showed epithelial nodules arising from the cystic lining and projecting into the cyst lumen. These nodules comprised epithelium with a plexiform or follicular pattern resembling that seen in intraosseous ameloblastoma. In both of these types, the cyst lining shows features of ameloblastoma but often in focal areas, and there is no evidence of infiltration of the fibrous tissue wall by ameloblastoma.

Type 3 – In the third variant, known as *mural unicystic ameloblastoma*, the presence in the connective tissue wall of the cyst, of invasive islands of ameloblastomatous epithelium which might (type 3b) or might not (type 3a) be connected to the cyst lining. Here also the cyst lining shows features of ameloblastoma in parts, but not throughout.

It is generally believed that the presence of tumour cells in the fibrous capsule of unicystic ameloblastoma, like in type 3 lesions, predisposes to recurrence after enucleation. It is also assumed that the behaviour of unicystic ameloblastoma with mural invasion is similar to that of its intraosseous counterpart. However, no study has clarified whether mural invasion can extend to the full-thickness of the fibrous capsule and beyond it into adjacent cancellous bone.

The prevalence of these various histological subtypes, and the behaviour of unicystic ameloblastoma with mural invasion in comparison with its conventional intraosseous counterpart have not been sufficiently documented in the literature.

Peripheral Ameloblastoma

A peripheral tumor is an odontogenic tumor with the histologic characteristics of an intraosseous ameloblastoma that occurs solely in the soft tissues covering the tooth-bearing parts of the jaws (Gardner, 1977)[24].

The peripheral or extraosseous ameloblastoma is the most rare variant of the ameloblastoma. This tumor probably arises from rests of dental lamina or the basal epithelial cells of the surface epithelium and shows the same features of the intraosseous form of the tumor (Woo et al., 1987)[25]. Clinically, these tumors present as nonulcerated sessile or pedunculated gingival lesions. Most examples are < 1.5 cm and usually occur over a wide age range, with an average reported age of 52 years. Although these tumors do not infiltrate bone, they may be seen to "cup out" bone in the jaws.

Malignant (Metastasizing) Ameloblastoma

Metastasizing (malignant) ameloblastoma distinguishes itself from ameloblastoma only by the presence of metastases. There are no specific histological differences compared to ameloblastomas that do not metastasize, and the diagnosis is made on clinical behaviour only. Metastatic deposits are mostly seen in the lung (75%), followed by cervical lymph nodes and spine (each almost 15%). Other locations, such as liver, skull, brain, kidney and small bowel, have also been reported, but with lower incidences (Laughlin, 1989)[26].

Treatment methods

Treatment of ameloblastoma is primarily surgical Treatment modalities for ameloblastomas are many and varied; they may be divided into conservative and radical therapies.

The management of the ameloblastoma by more conservative measures includes: enucleation[27, 22], enucleation and curettage[27], surgical excision and peripheral ostectomy[28], enucleation with liquid nitrogen cryotherapy[29], and enucleation with Carnoy's solution[30, 31].

The more radical treatment involves marginal resection, segmental resection, or composite resection.

Enucleation[27, 22]: refers to surgically shelling the lesion out of the bone. It is the separation of a lesion from bone, with preservation of bone continuity, by virtue of the lesion's containment within an encapsulating or circumscribing connective tissue envelope derived from the lesion or surrounding bone. The aim is to remove the whole cyst/tumour without leaving any visible remnants behind.

Curettage[27] is removal of a lesion from bone, with preservation of bone continuity, by scraping or morcellation necessitated by the friability of the lesion or absence of an intact encapsulating or circumscribing connective tissue envelope derived from the lesion or surrounding bone.

Marsupialization[32] (+ other modalities): This is also considered as exteriorization or decompression of the cyst, this refers to surgically removing the anterior bony wall of the lesion, and suturing the incised edge of the cyst/ tumour to the adjacent mucosa or skin. The authors explained that the bony wall fenestration was made as wide as possible, and after marsupialization, a prefabricated acrylic obturator was used to keep the window open. Patients were reviewed at 3-month intervals until they could withstand less aggressive treatment such as enucleation or curettage. If the marsupialization was effective in reducing the size of the lesion, it was followed by enucleation and curettage. If this was not the case, it was followed by resection.

Resection, the excision of a lesion that includes a measurable perimeter of investing bone. In the mandible this could be done with (segmental) or without (marginal) continuity defect (i.e. enbloc resection, or marginal mandibulectomy – with some safety margin and jaw continuity) or extend into a disarticulation if the temporomandibular joint is involved. In the maxilla it would be defined by the anatomic extension of the excision in subtotal (partial) or total maxillectomy (i.e. hemimandibulectomy, or partial maxillectomy—with some safety margin and loss of jaw continuity). The difference between resection with bone margin and segmental resection or maxillectomy was defined as whether or not the jawbone had lost its continuity. When surgeons agree that a resection should be performed, the most appropriate linear margin is still debated. Gold 1991 [33] believed that 3 cm is the most acceptable linear margin, while MacIntosh 1991 [34] recommended at least 1.5 cm, and preferably 2 cm bony margins for cure of this

neoplasm. A review of 82 ameloblastoma resections shows that this tumor extends with a range of 2 to 8 mm and a mean of 4.5 mm histologically beyond its radiographic demarcation on specimen radiographs (Gold and Upton 1991)[35]. The conclusion of this study is that a 1- to 1.5-cm bony linear margin provides a margin-free specimen that is curative provided remaining soft tissue margins are negative for tumor as well.

If microscopic remnants were expected to have been left behind, enucleation/curettage/marsupialization could be coupled with other treatment modalities such as application of chemical fixatives, electrocautery, cryotherapy or bone curettage.

Chemical fixative - Carnoy's solution[30, 31] *:* The bony cavity was then examined for any remaining tumour tissue which, if found, was removed. Carnoy's solution (chloroform 3 ml, absolute alcohol 6 ml, glacial acetic acid 1 ml, ferric chloride 1 g) was applied to the bony cavity for 3 min using cotton applicators or ribbon gauze soaked with Carnoy's solution. This was followed by copious irrigation with normal saline.

Cryosurgery[29] has been an alternative treatment modality for ameloblastoma. The aim of cryosurgery is to eliminate the invasive bone lesion without necessarily involving the problems of conventional anatomic radical surgery. Therefore the use of extreme cold temperature to manage ameloblastomas permits treatment of the bone in situ by devitalizing it and maintaining its inorganic matrix. There are four basic cryosurgery methods for use in the maxillofacial region: probe alone,

probe plus watersoluble jelly, liquid nitrogen coil, and liquid nitrogen spray. Each technique has advantages and disadvantages when applied to bone lesions of the jaws. However, probe plus water jelly and liquid nitrogen spray have been the most common freezing methods applied to bone lesions of the jaws. Liquid nitrogen spray is a potent and rapid freezing method that reaches a temperature of-198 °C within a few minutes. It can be used to treat large and irregular cavities in the jaws, but care must be taken to avoid necrosis of the surrounding soft tissue.

Bone curettage – peripheral ostectomy[28] - When the operator feels certain that all gross tumor has been removed, the peripheral ostectomy is initiated. A round craniotomy (acrylic) bur is utilized, and with a deliberate, overlapping approach, the remaining bone is ground away 2 to 3 mm beyond the visible margin. Dividing a large defect into sections with surgical packing will help ensure that no area will be overlooked. Some have advocated painting the margin with toluidine blue, which is then ground away; this also ensures that there are no skipped areas.

Clinical implications

The classification of any pathologic process should, under ideal circumstances, impart implications for treatment. In fact, treatment and prognosis, including cure rates, are all dependent upon the variant of the ameloblastoma. The multicystic ameloblastomas don't have capsule because imitating the dental sheet. Ameloblastomas may invade the intertrabecular spaces of cancellous bone but do

not invade compact bone, although they may erode it. This feature has a direct bearing on treatment. The variant plexiforme have better prognostic and radiography is unilocular. The follicular have worse prognostic (mainly the acanthomatous), radiography is multicystic and the desmoplasic may fibrosis. In general terms, the solid or multicystic variant is believed to be the most aggressive of the three variants, with relatively less aggressive behavior associated with the unicystic variant. With this statement in mind, those who advocate resection of the solid or multicystic ameloblastoma will commonly resort to enucleation and curettage of the luminal and intraluminal subtypes of the unicystic ameloblastoma. Under the circumstances the surgeon should routinely open a “cystic” lesion and look for luminal proliferation of tumor. Some authors have pointed to a similar biologic behavior between the solid or multicystic ameloblastoma and the mural subtype of the unicystic ameloblastoma, (Gardner, 1981;[36] Huffman and Thatcher, 1974[37]) thereby necessitating a similar approach with resection.

The management of the cystic ameloblastomas remains controversial. These lesions generally represent a less aggressive type of ameloblastoma and therefore should have a better prognosis. However, they may well be too destructive and infiltrative in their behavior to respond predictably to local enucleation or curettage. It would seem that if they are treated by a somewhat more aggressive method than enucleation or curettage, the prognosis should be considerably improved. A localized en bloc resection or enucleation and curettage supplemented by physical means, such as liquid nitrogen cryotherapy or Carnoy’s solution are suggest for management this variant.

The peripheral ameloblastoma is most appropriately treated with a wide local excision. When surgical margins are negative for tumor, cure is the likely consequence.

Several important factors ought to be considered in planning the treatment of ameloblastoma: It is important to distinguish among the three clinical types of ameloblastoma: the intraosseous solid or multicystic lesion; unicystic type; and the peripheral ameloblastoma because they require different forms of treatment.

References

1. Kramer IRH, Pindborg JJ, Shear M. WHO. Histological typing of odontogenic tumors. 2nd edn Berlin: Springer-Verlag 1992.

2. Eversole LR, Leider AS, Hansen LS. Ameloblastomas with pronounced desmoplasia. J Oral Maxillofac Surg 1984;42:735-40.

3. Waldron CA. Odontogenic cysts and tumors. In: Neville BW, Damm DD, Allen CM, et al, editors. Oral and maxillofacial pathology. 2nd ed. Philadelphia (PA): WB Saunders; 2002. p. 511-20.

4. Sapp JP, Eversole LR, Wysocki GP, editors. Contemporary oral and maxillofacial pathology. 2nd ed. St Louis (MO): Mosby; 2004. p. 136-43.

5. Philipsen HP, Reichart PA, Takata T. Desmoplastic ameloblastoma (including 'hybrid' lesion of ameloblastoma). Biological profile based on 100 cases from the literature and own files. Oral Oncol 2001;37:455–60.

6. Houston G, Davenport W, Keaton W, Harris S. Malignant (metastatic) ameloblastoma: report of a case. J Oral Maxillofac Surg 1993: 51: 1152–1155.

7. Ueno S,Nakamura S,Mushimoto K, Shirasu R. A clinicopathologic study of ameloblastoma. J Oral Maxillofac Surg 1986; 44:361–5.

8. Takahashi K,Miyauchi K, Sato K. Treatment of ameloblastoma in children. Br J Oral Maxillofac Surg 1998;36:453–6.

9. Nastri AL, Wiesenfeld D, Radden BG, et al. Maxillary ameloblastoma: a retrospective study of 13 cases. Br J Oral Maxillofac Surg 1995;33:28–32.

10. Jackson IT, Callan PP, Forte RA. An anatomical classification of maxillary ameloblastoma as an aid to surgical treatment. J Craniomaxillofac Surg 1996; 24:230–6.

11. Sehdev MK, Huvos AG, Strong EW, et al. Ameloblastoma of maxilla and mandible. Cancer 1974;33:324–33.

12. Komisar A. Plexiform ameloblastoma of the maxilla with extension to the skull base. Head Neck Surg 1984;7:172–5.

13. Barnes L, Eveson JW, Reichart P, Sidransky D. Pathology and genetics of head and neck tumors. Lyon: IARC Press 2005: pp. 284–327.

14. Müller H, Slootweg PJ. The growth characteristics of multilocular ameloblastomas. A histological investigation with some inferences with regard to operative procedures. J Maxillofac Surg 1985;13:224–30.

15. Philipsen HP, Reichart PA, Nikai H, et al. Peripheral ameloblastoma: biological profile based on 160 cases from the literature. Oral Oncol 2001;37:17-27.

16. Vickers RA, Gorlin RJ. Ameloblastoma: delineation of early histopathologic features of neoplasia. Cancer 1970;26:699–710.

17. Robinson L, Martinez MG. Unicystic ameloblastoma: A prognostically distinct entity. Cancer 1977: 40: 2278–2285.

18. Gardner DG, Corio RL. Plexiform unicystic ameloblastoma. A variant of ameloblastoma with a low recurrence rate after enucleation. Cancer 1984;53:1730–5.

19. Reichart PA, Philipsen HP, Sonner S. Ameloblastoma: biological profile of 3677 cases. Eur J Cancer Oral Oncol 1995; 31B:86–99.

20. Gardner DG, Morton TH,Worsham JC. Plexiform unicystic ameloblastoma of the maxilla. Oral Surg Oral Med Oral Pathol 1987;63:221–3.

21. Gardner DG. A pathologist's approach to the treatment of ameloblastoma. J Oral Maxillofac Surg 1984;42:161-6.

22. Leider AS, Eversole LR, Barkin ME. Cystic ameloblastoma. A clinicopathologic analysis. Oral Surg Oral Med Oral Pathol 1985: 60: 624–630.

23. Ackermann GL, Altini M, Shear M. The unicystic ameloblastoma: A clinicopathological study of 57 cases. J Oral Pathol 1988: 17: 541–546.

24. Gardner DG. Peripheral ameloblastoma: a study of 21 cases, including 5 reported as basal cell carcinoma of the gingiva. Cancer 1977;39:1625-33.

25. Woo SB, Smith-Williams JE, Sciubba JJ, Lipper S. Peripheral ameloblastoma of the buccal mucosa: case report and review of the English literature. Oral Surg Oral Med Oral Pathol 1987;63:78–84.

26. Laughlin EH. Metastasizing ameloblastoma. Cancer 1989: 64: 776–780.

27. Gardner DG, Corio RL. The relationship of plexiform unicystic ameloblastoma to conventional ameloblastoma. Oral Surg Oral Med Oral Pathol 1983: 56: 54–60.

28. Sachs SA. Surgical excision with peripheral ostectomy: a definitive, yet conservative, approach to the surgical management of ameloblastoma. J Oral Maxillofac Surg Clin North Am 1991;3:99-108.

29. Salmassy DA, Pogrel MA. Liquid nitrogen cryosurgery and immediate bone grafting in the management of aggressive primary jaw lesions. J Oral Maxillofac Surg 1995: 53: 784–790.

30. Lee PK, Samman N, Ng IO. Unicystic ameloblastoma—Use of Carnoy's solution after enucleation. Int J Oral Maxillofac Surg 2004: 33: 263–267.

31. Stoelinga PJ, Bronkhorst FB. The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. J Craniomaxillofac Surg 1988: 16: 184– 195.

32. Nakamura N, Higuchi Y, Tashiro H, Ohishi M. Marsupialization of cystic ameloblastoma: A clinical and histopathologic study of the growth characteristics before and after marsupialization. J Oral Maxillofac Sirg 53:748-54, 1995.

33. Gold L: Biologic behavior of ameloblastoma. Oral Maxillofac Surg Clin North Am 3:21, 1991

34. MacIntosh RB: Aggressive management of ameloblastoma. Oral Maxillofac Surg Clin North Am 3:73, 1991

35. Gold L, Upton GW, Marx RE: Standardized surgical terminology for the excision of lesions in bone: An argument for accuracy in reporting. J Oral Maxillofac Surg 49:1214, 1991

36. Gardner DG: Plexiform unicystic ameloblastoma: A diagnostic problem in dentigerous cysts. Cancer 47:1358, 1981

37. Huffman GG, Thatcher JW: Ameloblastoma—The conservative surgical approach to treatment: report of four cases. J Oral Surg 32:850, 1974

38. Pindborg JJ, Kramer IRH, Torloni H. WHO. Histological Typing of Odontogenic Tumours, Jaw Cysts, and Allied Lesions. Geneva: World Health Organization 1971.

39. Kramer IR. Ameloblastoma: A clinicopathological appraisal. Br J Oral Surg 1963: 35: 13–28.

40. Babarinde BA. Categorization of jaw ameloblastoma based on clinical Presentation. Br J Oral Maxillofac Surg 45 (2007) 433

41. Jackson I T, Callan PP, Robert A. Forté. An anatomical classification of maxillary ameloblastoma as an aid to surgical treatment. Journal of Cranio-Maxillofacial Surgery (1996) 24, 230-236

42. Sampson DE, Pogrel MA. Management of mandibular ameloblastoma: the clinical basis for a treatment algorithm. J Oral Maxillofac Surg 1999, 57:1074-1077.

43. Al-Bayaty HF, Murti PR, Thomson ERE, et al: Soft tissue recurrence of a mandibular ameloblastoma causing facial deformity in the temporal region: Case report. J Oral Maxillofac Surg 60:204, 2002

44. Nakasato S, Okamura S, Kudo K, et al: Gigantic ameloblastoma associated with secondary hypoproteinemia. J Oral Maxillofac Surg 49:764, 199

45. Stoelinga PJW, Bronkhorst FB. The incidence: multiple presentation and recurrence of aggressive cysts of jaws. J Craniomaxillofac Surg 1987: **15**: 184–195.

46. Holland PS, Mellor WC. The conservative treatment of ameloblastoma, using diathermy or cryosurgery. A 29-year review. Int J Oral Surg 1981: 10: 32–36.

47. Ueda M, Kaneda T. Combined chemotherapy and radiotherapy for advanced maxillary ameloblastoma. A case report. J Craniomaxillofac Surg 1991: 19: 272– 274.

Effect of Carnoy's solution on bone healing in experimental cavities in rat´s tibia

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ABSTRACT

The Carnoy's solution has been utilized in treatment of bones cavities after enucleation of maxillofacial cysts and tumor. The purpose of this study was to histologically analyze the influence of Carnoy's solution on bone healing in surgically created defects in rat tibias. This solution and physiological solution were inserted into surgical sites in rat tibia. After the observation periods of 14, 30, 60 and 90 days, according to the bioethic protocol, the animals were killed, the tibiae was removed and fixed in 10% formalin and decalcified in formic acid. After routine processing, the specimens were embedded in parafin for microtomy. Semi-serial sections 5 μm thick were cut in a transversal direction. The sections were stained with hematoxylin and eosin (HE) for analysis by light microscopy. The delay in tissue healing in the experimental group in relation to the control was noted in all the times after surgery. Analysis of the results demonstrated that the Carnoy's solution impaired the bone healing in rats tibiae.

Key Words: Carnoy's solution, ameloblastoma, keratocyst odontogenic tumor, bone healing

INTRODUCTION

Odontogenic Keratocysts Tumor (OKT) *(Ahlfors et al., 1984)* and Unicystic Ameloblastomas (UA) *(Robinson & Martines, 1977)* are known for their tendency to recur *(Punnia-Moorthy, 1989;Brondum & Jensen, 1991; Lau 7 Samman, 2006)*.

The recurrent OKT appear to support the notion that in a large number of OKTs, clusters of microcysts and epithelial islands are present in the mucosa, where the cyst is attached *(Chuong et. al.,1982)*. OKT that show orthokeratinization or mixed types of keratinization have less recurrence than parakeratinized cysts *(Browne, 1971; Bradley and Fisher, 1975; Bramley 1974; Crowley et al., 1992)*.

Because of the problematic nature of the cysts, many attempts have been made to reduce the high recurrence rate with improved surgical techniques. Some investigators advise tanning the cyst cavity with Carnoy's solution before enucleation of the cyst *(Willians & Connor, 1994; Woorsmit et. al., 1981)* or the use of the Carnoy's solution in the bone cavity after enucleation. *(Stoelinga 2001)*

Various treatment modalities for OKT have been used. These range from conservative to radical modes of treatment. The conservative approach includes decompression of the cysts followed by secondary enucleation *(Brandum & Jensen, 1991; Marker et. al., 1996; Tucker et. al., 1972)*, enucleation, curettage, cryosurgery *(Schmidt & Pogrel, 2001)* and application of Carnoy's solution. The more radical treatment involves marginal resection *(Bataineh and Al Qudah 1998)*, segmental resection *(Bramley et al., 1974)*, or composite resection *(Bataineh, 2000)*.

Unicystic ameloblastoma usually appears very similar to a non-neoplasic odontogenic cyst *(Isacsson et al., 1986)*. Three histologic variants of unicystic

ameloblastoma are described in the literature *(Robinson & Martinez, 1977; Ackermann et al., 1988)*. In the first type, luminal ameloblastoma, the tumor is confined to the luminal surface of the cyst. In the second type, intraluminal ameloblastoma, tumor nodules project from the cystic lining into the lumen of the cyst. In the third type, mural ameloblastoma, the fibrous wall of the cyst is infiltrated with tumor nodules. The third type is considered the most aggressive of the 3 variants, reported in the literature for mural unicystic ameloblastomas.

There has been some debate regarding the most appropriate method for surgical removal of this tumor. Various treatment modalities for unicystic ameloblastoma have been used, such as segmental or marginal resection as normally used for conventional ameloblastoma, however, more conservative treatments have frequently been reported. Enucleation *(Gardner & Corio, 1983; Leider et. al., 1985, Robinson & Martinez 1977; Shteyer et al., 1978)* and curettage *(Gardner & Corio, 1983)* are mostly chosen. Some clinicians used marsupialization *(Nakamura et. al., 2002; Nakamura et al., 1995)* to reduce the size of the lesion, followed by second stage surgery. These treatments can be followed by adjunctive therapy, including cryotherapy *(Holland & Mellor 1981; Marciani et al., 1977; Pogrel, 1993, Salmassy & Pogrel, 1995)*, thermal *(Holland & Mellor 1981)* or chemical cauterization using Carnoy's solution *(Lee et. al., 2004; Stoeling & Bronkhorst, 1988)* and even radiotherapy *(Anastassov et al., 1998; Atkinson et al., 1984; Gardner 1988, Sheinkopf & Friedman, 1990)* and chemotherapy *(Ueda & Kaneda, 1991)*.

Carnoy's solution (chloroform 3 ml, absolute alcohol 6 ml, glacial acetic acid 1 ml, ferric chloride 1 g) was described as a sclerozing agent for the treatment of cysts and fistulae *(Culter & Zollinger, 1933)* and remains in use today after enucleation of unicystic ameloblastoma and OKT in bony cavity for effectiveness against residual pathology for

diminish the risk of recurrence this lesions. Treatment of the bone cavity after enucleation of cysts and tumors with Carnoy's solution is helpful to prevent any remmants that are left from developing into recurrence, but it may also damage adjacent bone *(Zhao et al., 2002)*.

The objective of this study was to assess the effects of Carnoy's solution on osseous repair in rat tibia, aiming to observe the presence of inflammatory cells and new osseous tissue formation.

MATERIAL AND METHODS

Experimental animals

The study animals (30) were 3-month-old rats (*Rattus norvegicus, albinus, Wistar)* weighing 200–300 g were obtained from our own breeding colony and maintained on rat chow and tap water *ad libitum.* All animals were fed an ordinary diet of rodent feed (Labina, Agribands Purina, São Paulo, Brazil). They were housed in a room kept at constant temperature (23±1°C) and on a 12-hour-light/12-hour dark (lights on at 7:00 A.M.) schedule.

The use of animals was approved by the local Animal Research Ethics Committee, and the animals kept in an appropriate facility located in the São Paulo University. The experimental protocol conforms with ethical principles in animal research adopted by Brazilian College of Animal Experimentation (COBEA) and was approved by Biomedical Sciences Institute/University of São Paulo – Ethical Committee for Animal Research (CEEA).

Surgical method

Anesthetic induction was accomplished by intraperitoneal injection of ketamine (15mg/kg) and xylazine (3mg/kg). After shaving and aseptic preparation of the operative site, a linear 15 mm incision was made on the right tibia and full thickness flaps were reflected. Sterile carbide round burs nº 2 were used in a high-speed handpiece under continuous sterile saline irrigation to create two unicortical defects on the anterolateral surface of the rigth tibia (Figure. 1).

The osseous defect was filled with Carnoy's solution (chloroform 3 ml, absolute alcohol 6 ml, glacial acetic acid 1 ml, ferric chloride 1 g) and physiological solution which were removed after 3 minutes. The soft tissues were then repositioned carefully and sutured (deep and superficial sutures) to achieve primary closure (Nylon 6-0, Ethicon, São Paulo, Brazil).

Figure 1 – Intraoperative field - Two unicortical defects on the anterolateral surface of the rigth tibia.

Tissue processing

Animals were sacrificed at 24 hs, 7, 14, 30, 60 and 90 days post-operative by prolonged anesthesia and tibiae were explanted for histological analysis. The tibias were removed and fixed in 10% formalin, decalcified, processed and embedded in paraffin. Semi-serial sections 5 μm thick were cut in a transversal direction. The sections were stained with hematoxylin and eosin (HE) for analysis by light microscopy.

RESULTS

In optical microscope the sheets were observed from the smallest to the largest increase. The analysis was made in a descriptive way by the observer and the collected data were logged simultaneously for subsequent organization. The identification of the experimental groups (controls or Carnoy) it was not revealed to the observer.

All of the specimens presented bone with pattern of normal organization, with a small superficial gap in osseous cortical. This space was filled out with healing tissue in several steps of maturation, extending from the cortical to the medular bone.

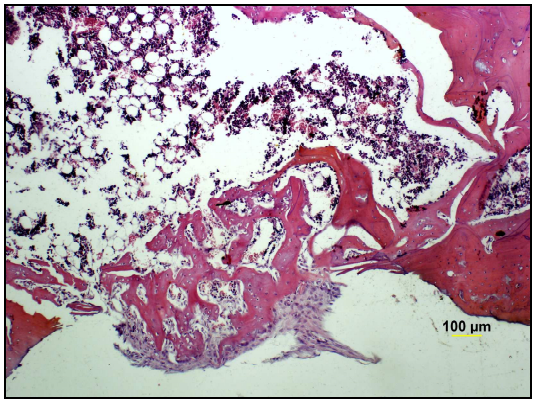
The presence of inflammatory cells and the formation of connective tissue and osseous tissue in the rat tibiae were considered in the histological analysis of the specimens of the Control and Carnoy's groups.

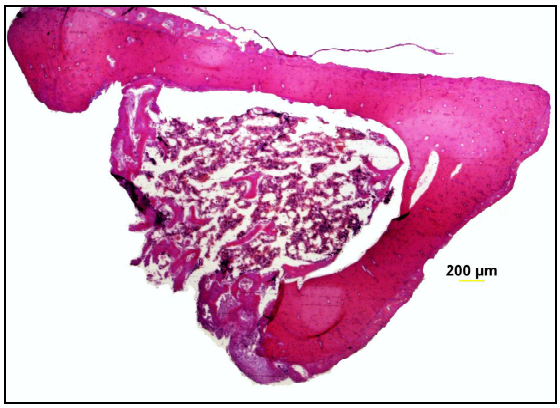
In the specimens obtained in the times of 24 hours and seven days the healing tissue just presented vascular neoformação and infiltrated inflammatory composed mainly by polimorfonuclears (24 hours) and mononuclears cells (7 days). Because of not relevant data to demonstrate, images of those experimental times were not collected, we just told as registration of the phase of the research.

Most of the specimens presented small amount of fatty tissue that she showed permeated to the rich arrangement of fibers grooved skeletal of the muscular plan or randomized disposed by the connective tissue.

In experimental times of 14, 30, 60 the cuts showed a gradual process of slow bone woven, when we compared the same times for the group control (Figure 2). To the 60 days de post-operative, we could verify the presence of mineralized bone with lines different from growth (reversion).

In the experimental group of 90 days (Carnoy's group) we found the presence of ossification endocondral still in mineralization process, presenting small areas or mineralization focuses, as well as areas of osteoid tissue (Figure 3, A, B, C e D).





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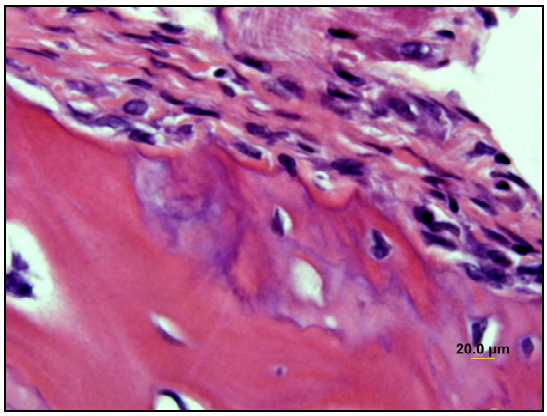

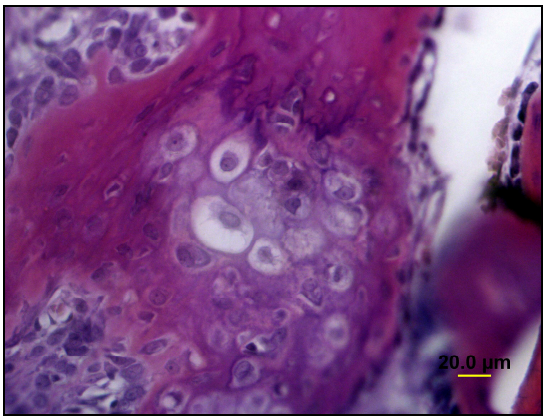

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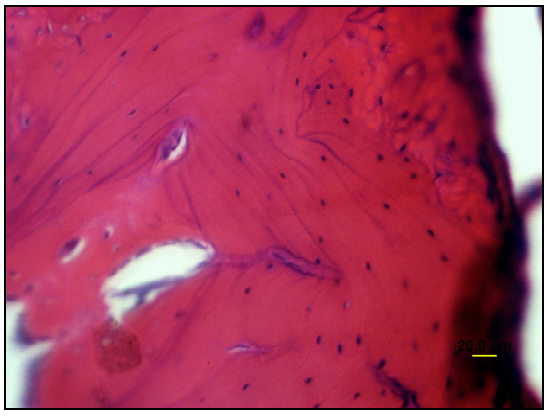
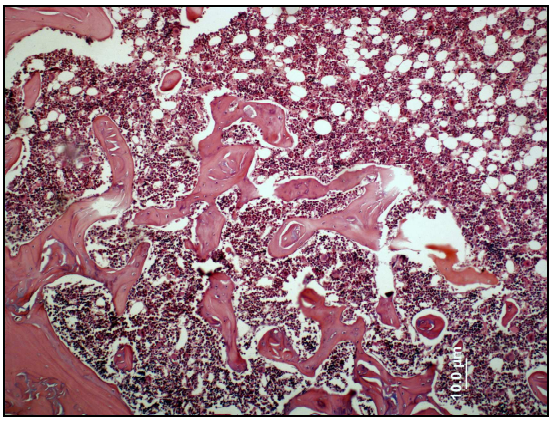
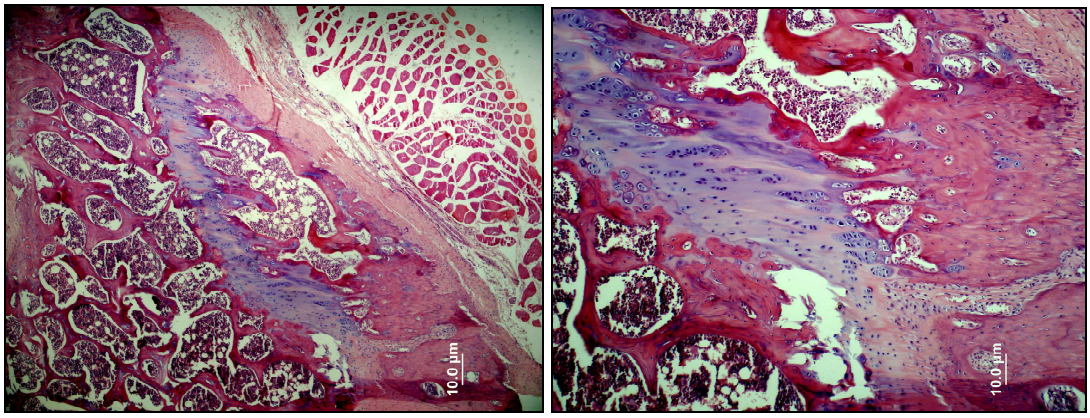


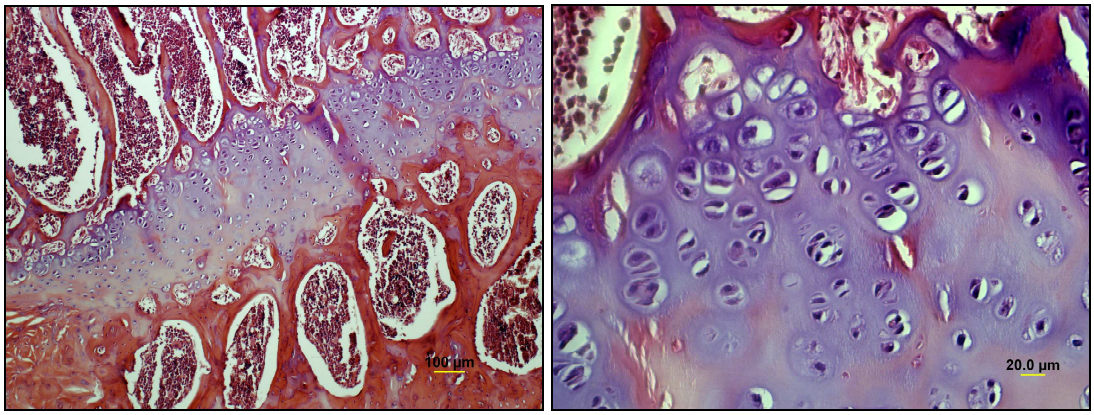


E F

Figure 2 – Microscopic aspects of the bone repair in the times at 14 days (Control group control in A, Carnoy's group in B); 30 days (Control group in C, Carnoy's group in D); 60 days (Control group in E, Carnoy's groups in F), HE



A B



C D

Figure 3 – Microscopic aspects of the bone repair in the experimental time of 90 days. In A and B we observed the presence of the bone defect filled out by cartilaginous and bone woven. In C and D the details of the process are verified, HE

In analysis of the obtained data it was used statistical descriptive with the use of tables with data of absolute and relative frequencies. After 21 days all of the analyses were repeated for application of the index Kappa (Landis and Koch, 1977), used for evaluation as for the level of a same observer's agreement, in agreement with the illustration below:

Kappa coefficient	**Agreement level**
0,00	-
0,00 – 0,20	Low
0,21 – 0,40	Médium
0,41 – 0,60	Moderate
0,61 – 0,80	Substantial
0,81 – 1,00	Almost perfect

The following aspects were prioritized, considered relevant:

a) Presence of areas of endocondral ossification in mineralization phase:

For this criterion the Kappa index resulted in 0,85, with agreement level classified as "almost perfect";

b) Presence of reversion lines and ripe osteócitos:

For this criterion the Kappa index resulted in 0,89, being the agreement level classified as "almost perfect."

DISCUSSION

In the present study, we demonstrated that local application of Carnoy's solution impairment the bone formation in rat tibiae experimental bone defects. Carnoy's solution, a powerful tissue fixative that can penetrate bone to 1,54 mm *(Voorsmit, 1985)*. Carnoy's solution is, therefore, also likely to penetrate cancellous spaces and thus devitalize and fix the remaining tumor cells. The success of the application of this agent after enucleation was thought to be due to both its penetration and fixation action *(Lau & Samman, 2006)*.

The control areas presented significantly more bone formation than the areas that received Carnoy's solution. This was probably due to the disturbance of the physiologic bone turnover and healing response at 14, 30, 60 and 90 days in the cavity selected as the experimental model.

The original description on the use of Carnoy's solution was to place it into the cyst lumen before enucleation *(Voorsmit, Stollinga, Van Hallst 1981)*. Because most clinicians apply it to the bony cavity after enucleation, it is unclear whether the same results can be expected. In addition, there was not a systemic recording of the complications associated with its use. Adding Carnoy's solution to the cyst cavity for 3 minutes after enucleation results in a recurrence rate comparable to that of resection without unnecessarily aggressive surgery *(Stoelinga and Bronkhorst, 1988).*

Further studies on the depth of invasion, possibly into adjacent bone, are needed to correlate with the use of Carnoy's solution and the duration of contact between Carnoy's solution and the bony cavity for effectiveness against residual pathology after enucleation of unicystic ameloblastoma and Odontogenic keratocysts.

In the present study, the control defects were completely repaired by bone at 30 days post-operative demonstrating that they were not ‘critical size’ defects. According to Schmitz & Hollinger (1986), ‘critical size’ defects are defined as defects of a size that precludes spontaneous bone regeneration/healing during the lifetime of the animal. The defects surgically created in the present study measured 4mm in length and 3mm in width. This experimental model was based on the work of Lewandrowski et al. (1999) in another animal study. According to the authors, 3mm diameter defects surgically created in rat tibias did not heal spontaneously in the control group throughout the experimental period (up to 7 weeks post-operative). They stated that these were critical size defects. Based on their observations, Lewandrowski et al. (1999) stated that both the animal model selected and the defects surgically created were appropriate for comparative histological evaluations. Although we used surgically created defects with greater dimensions than those used by Lewandrowski et al. (1999), the defects of the control Group in this study were completed repaired by bone at 30 days postoperative. One possible explanation for this could be that we used a different rat species.

One limitation of the rat tibia model used in this study is that small dimensions of bone defects. In general, the bone defects created after enucleation of keratocysts and ameloblastomas in human mandible are highter dimensions. If the Carnoy’s solution had utilized in this defects, it can not healing in post-operative time. The healing after removal of benign cysts and tumors of the jaws was studied radiographicaly *(Kawai et al., 1995)*. Not exist reported of mandibular fractures associated with used of Carnoy’s solution, but this possibility not may be excluded. In the future, these problems can be controlled by using larger animals. Is necessary to be elucidate the relationship between the mandibular mechanical function and the bone quality.

CONCLUSION

Within the limits of this study, it can be concluded: (a) the control groups had significantly more new bone formation than Carnoy's groups at 14, 30, 60 and 90 days post-operative and (b) at 90 days post-operative, the Carnoy's groups had delayed of bone formation. The application of Carnoy's solution in bone defects did harm osteogenesis.

In summary, the Carnoy's solution used in this study delayed bone healing in 'non-critical size' defects.

REFERENCES

Ahlfors E, Larsson A, Sjogren S. The odontogenic keratocyst: a benign cystic tumor? J Oral Maxillofac Surg 1984: 42:10–19.

Robinson L, Martinez MG. Unicystic ameloblastoma: A prognostically distinct entity. Cancer 1977: 40: 2278–2285.

Punnia-Moorthy A. An unusual late recurrence of unicystic ameloblastoma. Br J Oral Maxillofac Surg 1989: 27: 254–259.

Lau SL, Samman N: Recurrence related to treatment modalities of unicystic ameloblastoma: a systematic review. Int. J. Oral Maxillofac. Surg. 2006; 35: 681– 690.

Brondum N, Jensen VI. Recurrences of keratocysts and decompression treatment: a long-term follow-up of forty-four cases. Oral Surg 1991: 72: 265–269.

Browne RM. The odontogenic keratocyst: Histologic features and their correlation with clinical behaviour. Br Dent J 1971: 131: 249–259.

Crowley TE, Kaugars GE, Gunsolley JC. Odontogenic keratocysts: A clinical and histological comparison of the parakeratin and orthokeratin variants. J Oral Maxillofac Surg 1992: 52: 22–26.

Chuong R, Donoff RB, Guralnick W. The odontogenic keratocyst. J Oral Maxillofac Surg 1982: 40: 787–802.

Ackermann GL, Altini M, Shear M: The unicystic ameloblastoma: A clinicopathologic study of 57 cases. J Oral Pathol 17:541, 1988

Takahashi K, Miyauchi K, Sato K: Treatment of ameloblastoma in children. Br J Oral Maxillofac Surg 36:453, 1998

Shigeru U, Mushimoto K, Shirasu R: Prognostic evaluation of ameloblastoma based on histologic and radiographic typing. J Maxillofac Surg 47:11, 1989

Olaitan AA, Adeola DS, Adekeye EO: Ameloblastoma: Clinical features and management of 315 cases from Kaduna, Nigeria. J Craniomaxillofac Surg 21:351, 1993

Bataineh AB: Effect of preservation of the inferior and posterior borders on recurrence of ameloblastomas of the mandible. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:155, 2000

Gardner DG, Corio RL. The relationship of plexiform unicystic ameloblastoma to conventional ameloblastoma. Oral Surg Oral Med Oral Pathol 1983: 56: 54–60.

Leider AS, Eversole LR, Barkin ME. Cystic ameloblastoma. A clinicopathologic analysis. Oral Surg Oral Med Oral Pathol 1985: 60: 624–630.

Shteyer A, Lustmann J, Lewin- Epstein J. The mural ameloblastoma: A review of the literature. J Oral Surg 1978: 36: 866–872.

Nakamura N, Higuchi Y, Mitsuyasu T, Sandra F, Ohishi M. Comparison of long-term results between different approaches to ameloblastoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002: 93: 13–20.

Nakamura N, Higuchi Y, Tashiro H, Ohishi M. Marsupialization of cystic ameloblastoma: A clinical and histopathologic study of the growth characteristics before and after marsupialization. J Oral Maxillofac Surg 1995: 53: 748–754 (discussion 755–746).

Holland PS, Mellor WC. The conservative treatment of ameloblastoma, using diathermy or cryosurgery. A 29-year review. Int J Oral Surg 1981: 10: 32–36.

Marciani RD, Trodahl JN, Suckiel MJ, Dubick MN. Cryotherapy in the treatment of ameloblastoma of the mandible: Report of cases. J Oral Surg 1977: 35: 289–295.

Pogrel MA. The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions. J Oral Maxillofac Surg 1993: 51: 269–273 (discussion 274).

Salmassy DA, Pogrel MA. Liquid nitrogen cryosurgery and immediate bone grafting in the management of aggressive primary jaw lesions. J Oral Maxillofac Surg 1995: 53: 784–790.

Lee PK, Samman N, Ng IO. Unicystic ameloblastoma—Use of Carnoy's solution after enucleation. Int J Oral Maxillofac Surg 2004: 33: 263–267.

Stoelinga PJ, Bronkhorst FB. The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. J Craniomaxillofac Surg 1988: 16: 184–195.

Anastassov GE, Rodriguez ED, Adamo AK, Friedman JM. Case report. Aggressive ameloblastoma treated with radiotherapy, surgical ablation and reconstruction. J Am Dent Assoc 1998: 129: 84–87.

Atkinson CH, Harwood AR, Cummings BJ. Ameloblastoma of the jaw. A reappraisal of the role of megavoltage irradiation. Cancer 1984: 53: 869–873.

Gardner DG. Radiotherapy in the treatment of ameloblastoma. Int J Oral Maxillofac Surg 1988: 17: 201–205.

Sheinkopf DE, Friedman JM. Radiotherapy in the management of recurrent ameloblastoma. A long-term follow-up of a case. N Y State Dent J 1990: 56: 36–37.

Ueda M, Kaneda T. Combined chemotherapy and radiotherapy for advanced maxillary ameloblastoma. A case report. J Craniomaxillofac Surg 1991: 19: 272– 274.

Beadley PF, Fisher AD. The cryosurgery of bone. An experimental and clinical assessment. Br J Oral Surg 1975: 13: 111–127.

Bramley P. The odontogenic keratocyst—an approach to treatment. Int J Oral Surg 1974: 3: 337–41.

Culter EC, Zollinger R. Sclerosing solution in the treatment of cysts and fistulae. Am J Surg 1933: 19: 411–418.

Schmitz, J.P. & Hollinger, J.O. (1986) The critical size defect as an experimental model for craniomandibulofacial nonunions. Clinical Orthopaedics and Related Research 205: 299–308.

Lewandrowski, K-U., Cattaneo,M.V., Gresser, J.D., Wise, D.L., White, R.L., Bonassar, L. & Trantolo, D.J. (1999) Effect of a poly (propylene fumarate) foaming cement on the healing of bone defects. Tissue Engineering 5: 305–316.

Kawai T, Murakami S, Hiranuma H, Sakuda M. Healing after removal of benign cysts and tumors of the jaws – A radiologic appraisal. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;79:517-25

Williams TP, Connor FA Jr. Surgical management of the odontogenic keratocysts: aggressive approach. J Oral Maxillofac Surg 1994;52:964-6.

Woorsmit RACA, Stoelinga PJW, van Haelst VJGM. The management of keratocysts. J Maxillofac Surg 1981;9:228-36.

Schmidt BL, Pogrel MA. The use of enucleation and liquid nitrogen cryotherapy in the management of odontogenic keratocysts. J Oral Maxillofac Surg 2001;59:720-5.

Brandum N, Jensen VJ. Recurrence of keratocysts and decompression treatment: a long-term follow-up of forty-four cases. Oral Surg Oral Med Oral Pathol 1991;72:265-9.

Marker P, Brondum N, Clausen PP, Bastian HL. Treatment of large odontogenic keratocysts by decompression and later cystectomy. cystectomy. A long-term follow-up and a histologic study of 23 cases. Oral Surg Oral Med Oral Pathol 1996;82:122-31.

Tucker WM, Pleasants JE, MacComb WS. Decompression and secondary enucleation of a mandibular cyst: report of case. J Oral Surg 1972;30:669-73.

Bramley P. The odontogenic keratocyst: an approach to treatment. Int J Oral Surg 1974;3:337-41.

Ephros H, Lee HY. Treatment of a large odontogenic keratocyst using the Brosch procedure. J Oral Maxillofac Surg 1991;49: 871-4.

Bataineh AB, Al Qudah MA. Treatment of mandibular odontogenic keratocysts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:42-7.

Isacsson G, Andersson L, Forsslund H, Bodin I, Thomsson M. Diagnosis and treatment of the unicystic ameloblastoma. Int J Oral Maxillofac Surg 1986: 15: 759–764.

Stoelinga PJW.: Long-term follow-up on keratocysts treated according to a defined protocol. Int. J. Oral Maxillofac. Surg. 2001; 30: 14–25.

Frerich B, Cornelius CP, Wietholter H. Critical time of exposure of the rabbit inferior alveolar nerve to Carnoy's solution. J Oral Maxillofac Surg 1994: 52: 599–606.

Voorsmit R. The incredible keratocyst: A new approach to treatment. Dtsch Zahnarztl Z 1985: 40: 641.

Culter E, Zollinger R. Sclerosing solution in the treatment of cysts and fistulae. Am J Surg 1933: 19: 411.

Landis JR; Koch GG. The measurement of observer agreement for categorical data. Biometrics, v.33, n.1, p.159-74, Mar. 1977.

Woolgar JA, Rippin JW, Browne RM. A comparative study of the clinical and histological features of recurrent and nonrecurrent odontogenic keratocysts. J Oral Pathol 1987;16:124-8.

Voorsmit RACA. The incredible keratocyst: a new approach to treatment. Deutsche Zahnarztliche Zeitschrift 1985;40:641-4.

Voorsmit RA, Stollinga PT, Van Hallst VJ. The management of keratocysts. J Maxillofac Surg 1981;9:228-36.

Stoelinga PJW, Bronkhorst FB. The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. J Craniomaxillofac Surg 1988;16:184-95.

Discussão geral

Esses artigos são resultados do processo de formação docente, nível de Doutorado em Cirurgia e Traumatologia Bucomaxilofaciais, pelo Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul. PUCRS.

O primeiro deles abordou o novo paradigma em Pesquisa Odontológica, isto é, a Odontologia Baseada em Evidências. Aplicando os princípios da medicina baseada em evidências para Odontologia, a America Dental Association desenvolveu a seguinte definição para o termo “odontologia baseada em evidências” significando uma abordagem para os cuidados de saúde bucal que requer uma integração prudente de avaliações sistemáticas das evidências científicas clinicamente relevantes, relacionando as condições médicas e bucais do paciente, com a experiência clínica do dentista juntamente com as necessidades e preferências do paciente.

O dentista pode tomar decisões clínicas baseados no *grau de crença* que têm sobre o curso de determinada doença e na eficácia de determinado tratamento. Essa crença muitas vezes não tem sequer plausibilidade biológica convincente, derivando apenas de tradição cultural ou gosto pessoal.

O mais comum é a decisão tomada com base somente na *plausibilidade biológica*. Nesse caso, o profissional recorre aos seus conhecimentos sobre as disciplinas básicas como anatomia, fisiologia, patologia, entre outras. Ele acredita que o conhecimento sobre os mecanismos da doença e de funcionamento do organismo e do comportamento dos materiais são suficientes para concluir qual é o melhor tratamento numa determinada situação clínica. Ou seja, o profissional analisa os riscos baseados em propriedades físicas e químicas. A referência ao desenho físico, a um mecanismo ou a um

traço que determina o risco de um evento é a essência da avaliação do risco baseado na plausibilidade biológica.

Uma terceira forma de tomar decisão clínica se baseia num outro entendimento de risco ou incerteza; risco baseado em *freqüência*. Nesse caso, a informação para tomada de decisão clínica é baseada em um número grande de observações sistemáticas e é a freqüência relativa de um evento em um grupo de referência. Para um frequentista, senão há grupo de referência, não é possível inferir probabilidade. Para um frequentista, risco se refere somente a situações para as quais há uma quantidade grande de dados empíricos.

Podemos então identificar três abordagens de avaliação de risco para a tomada de decisão clínica: tradicionalista/dogmática – baseada em tradição cultural e gosto pessoal; mecanista – baseada no mecanismo de funcionamento do organismo e dos materiais. Frequentista – baseada em um número grande de observações sistemáticas. A odontologia baseada em evidências enfatiza uma abordagem frequentista de avaliação de risco para a tomada de decisão clínica.

Particularmente, como demonstrado no primeiro artigo, nas especialidades cirúrgicas há limitações no desenho de estudos que promovem fortes evidências científicas. A maioria dos trabalhos em cirurgia bucomaxilofacial usa como desenhos experimentais, séries-de-casos, estudos coorte, estudos prospectivos e estudos retrospectivos. Esses modelos de pesquisa é que estão sendo preferidos para publicação. Entretanto, para realização de tais estudos, os procedimentos cirúrgicos devem ser protocolados e os pesquisadores devem dispor de um banco de dados sobre os pacientes atendidos. O seguimento à longo prazo do paciente é fundamental para geração e análise confiável dos dados. São várias as dificuldades para se realizar esses estudos, que devem ser superadas para confecção de artigos científicos com maior grau de evidência científica.

Considerando que o ameloblastoma não é um tumor muito freqüente e que a proservação e seguimento dos pacientes é de longo prazo, pelo menos 10 anos havendo relatos de recidiva após 21 anos, estudos multicêntricos devem ser incentivados para avaliação de resultados de tratamentos e recidiva da lesão. Com a possibilidade que a informática e internet proporcionam um banco de dados internacional para lesões raras pode ser proposto e concretizado num futuro próximo. A integração dos pesquisadores e a troca de informações científicas a respeito de determinado assunto, pode passar das publicações em periódicos, a grupos conectados on-line.

Para os neófitos em pesquisa cirúrgica este trabalho é um parâmetro inicial para auxílio na preparação e condução dos projetos científicos na área de cirurgia e traumatologia bucomaxilofacial, melhorando a qualidade do conhecimento produzido em trabalhos futuros que certamente terão estratégias para diminuir viés e erros, aumentando a validade dos resultados.

O segundo artigo, uma revisão sobre ameloblastoma, ilustra as dificuldades para se conseguir boas evidências para determinar qual o melhor tratamento para essa lesão. Não há consenso na literatura, e ainda não é possível definir estatisticamente qual dos tratamentos é o melhor. Nesse caso específico, ainda prevalece, a opinião dos especialistas juntamente com a necessidade e preferência pelo tratamento do paciente. A dificuldade de se comparar a freqüência de resultados de tratamentos no caso desse tumor é que a série depende de longos períodos de tempo e de seguimento. Estratégias como desenhos do tipo caso-controle e estudos coorte podem ser utilizados.

As características anatomopatológicas do tumor determinam o comportamento clínico da lesão, no que se refere a recidivas. Entretanto, o tratamento cirúrgico está diretamente ligado ao prognóstico do paciente. A utilização de uma técnica cirúrgica

adequada, considerando os aspectos patológicos da lesão é fundamental no tratamento desses pacientes.

Há outros fatores que influenciam na indicação de determinada técnica cirúrgica, além das características patológicas, e são: o tamanho do tumor, a agressividade, a localização do tumor, se na maxila ou na mandíbula, na região anterior ou posterior, a idade do paciente, a raça, entre outros.

Pesquisas em pacientes com ameloblastomas podem ser melhoradas com a formação de um banco de dados, que incluam todos os dados dos pacientes, fotos, exames, e o seguimento desse paciente. A Universidade com programas de pós-graduação em Cirurgia Bucomaxilofacial é a instituição que reúne condições para formação desse banco de dados. Além das características de diagnóstico e tratamento do ameloblastoma, pesquisas sobre à qualidade de vida do paciente e técnicas de reconstrução são necessárias. A alta morbidade dos tratamentos mais agressivos pode ser avaliada considerando a qualidade de vida do paciente e sua percepção dos resultados do tratamento. Por se tratar de um tumor benigno é importante considerar esses dados.

Um esforço internacional entre os especialista deve ser realizado no sentido de unificar a terminologia e padronizar os procedimentos afim de se ter melhores parâmetros comparativos na literatura.

O exame anatomopatológico deve seguir a classificação atualmente vigente, seguindo os critérios de Virkers e Gorlin 1977, para tipificação do ameloblastoma, principalmente no tipo unicístico que pode apresentar três variantes com implicações no prognóstico e tratamento.

A pesquisa sobre reparo ósseo em cavidades expostas a solução de Carnoy descreve as alterações ósseas que podem ser esperadas clinicamente quando se utiliza essa

solução nas cavidades ósseas. Tal tratamento já é aplicado em humanos, entretanto, não havia na literatura uma descrição do que ocorria com o tecido ósseo. Trata-se de pesquisa pura, que esclarece uma prática clínica, já preconizada na literatura.

Futuras pesquisas devem ser realizadas comparando os efeitos da solução de Carnoy com a Crioterapia. Ainda não há estudos comparativos que esclareçam qual das técnicas é a melhor. Os tempos de aplicação da solução de Carnoy também podem ser estudados, bem como a invasão do tumor ao osso adjacente.

Repercussão do trabalho

A produção e divulgação do conhecimento ficam representadas nessas publicações. Além do valor científico, todo o caminho para se chegar à finalização dos artigos contribuiu na formação do aluno de pós-graduação; alicerçando a metodologia, senso crítico, capacidade de realização e transposição das dificuldades.

O envolvimento de uma equipe nessas pesquisas tem valor didático pedagógico, pois reúne com foco num tema de pesquisa, alunos de graduação, alunos de pós-graduação e professores orientadores. Essa convivência proporciona o ensino além da sala de aula. Desenvolvendo e preparando alunos para resolução de questões relevantes para a sociedade.

A partir do momento que se melhora a formação de recursos humanos, o conhecimento adquirido se estende aos pacientes que se beneficiam dos novos conhecimentos desses profissionais.

Publicar o que se produz num programa de pós-graduação rende pontos ao curso, aumentando sua nota nos órgãos de avaliação, ampliando a credibilidade para satisfação da demanda de fomentos e bolsas de estudo.

O Pilar Triplo da Universidade é: Ensino, Pesquisa e Extensão. A isso se acrescentam:

- Interação entre o professor e estudante

- Interação entre cursos diversificados e específicos

Interação entre o estudante universitário e cursos pós-graduados

- Interação entre a universidade e público e setores privados

Acima de tudo, a atividade principal da Universidade é preparar recursos humanos qualificados e competentes para que satisfaça as necessidades da sociedade. Sempre surge o assunto de pesquisa pura versus pesquisa aplicada. Eles não deveriam ser

considerados separadamente. Essas pesquisas representam a procura contínua para conhecimento e a produção científica. Há os que defendem que a pesquisa não deveria ser restringida à academia, mas deveria ser convertida em produtos ou serviços à sociedade. Outros sustentam que a universidade deveria praticar nível alto pesquisa acadêmica independentemente da aplicação prática de resultados. Os dois pontos de vista não deveriam ser considerados separadamente.

Programas pós-graduados têm como objetivo qualificar professores e pesquisadores. Como este processo começa? Certamente não há um produto prático para beneficiar sociedade. Pesquisa, em seu nível inicial, é essencialmente acadêmica. O papel da universidade é, antes de qualquer outra coisa, a qualificação de profissionais altamente competentes que, sob supervisão de pesquisadores orientadores, produzam conhecimento e qualifique outros pesquisadores. Os pesquisadores orientadores deveriam ser hábeis para suprir às necessidades do mercado e registrar patentes.

Há os que dizem que “toda pesquisa científica deveria ter sua aplicabilidade e um impacto designado; caso contrário, é inútil e, muitas vezes, um desperdício de recursos.”

Entretanto, a experiência acadêmica, especialmente em nível pós-graduado, provou que a prática efetiva de pesquisa (até mesmo se não é aplicada) contribuiu para a qualificação de profissionais competentes para servir a universidade. Melhorou ensino e atividades de pesquisa, inclusive a melhoria da prática profissional. Além disso, ensina a todo estudante que descobertas médicas e inovações resultam de diligente investigação científica conduzida pelo trabalho cotidiano em laboratórios, hospitais e universidades.

Referências

Goldenberg S. The objectives of the university. Editorial. Acta Cirúrgica Brasileira - Vol. 23 (5) 2008 - 400

Luiz RR, Costa AJL, Nadanovsky P. Epidemiologia e Bioestatística na Pesquisa Odontológica. Atheneu. São Paulo, 2005.

Day Robert A. Como escrever e publicar um artigo científico. 5ª edição. Editora Santos. São Paulo, 2001 275p.

Hulley, Stephen B. Delineando a pesquisa clínica: uma abordagem epidemiológica/ Stephen B. Hulley, Steven R. Cummings, Warren S. Browner, Deborah Grady, Norman Hearst, Thomas B Newman; trad. Michel Schmidt Duncan e Ana Rita Peres. - 2ª ed. – Porto Alegre: Artmed, 2003.

ACADEMIA BRASILEIRA DE LETRAS - Vocabulário ortográfico da língua portuguesa, 3a. ed. Rio de Janeiro, Imprensa Nacional, 1999.

Cláudio Moreno. O emprego do hífen: sócio-econômico. Disponível em: http://www.sualingua.com.br/06/06_socio_economico.htm. Acessado: 31 de janeiro de 2007.

Jornal do Site. Regulamentação de especialidade profissional – Cirurgia e Traumatologia Buco-maxilo-facial. Disponível em:

http://www.jornaldosite.com.br/arquivo/leisaude/bucomaxilo.htm. Acessado em 31 de janeiro de 2007.

Não tropeçe na língua. Socioeconômico e socio-econômico. Disponível em: http://www.tj.ro.gov.br/emeron/sapem/2002/outubro/2510/PORTUGUES/P01.htm. Acessado em 31 de janeiro de 2007.

Linguagem médica. Hífen em termos médicos. Disponível em:: http://usuarios.cultura.com.br/jmrezende. Acessado em 31 de janeiro de 2007.

ANEXOS

Comissão Científica e de Ética
Faculdade da Odontologia da PUCRS

Porto Alegre 28 de outubro de 2008

O Projeto de: ***Tese***

Protocolado sob nº:	0053/08
Intitulado:	Efeitos da solução de Carnoy no reparo ósseo em cavidades experimentais de tíbias de ratos
Pesquisador Responsável:	Prof. Dr. Rogério Miranda Pagnoncelli
Pesquisadores Associados	André Takahashi
Nível:	Doutorado

Foi ***aprovado*** pela Comissão Científica e de Ética da Faculdade de Odontologia da PUCRS em *08 de outubro de 2008.*

Prof. Dr. Eraldo Luiz Batista Júnior
Presidente da Comissão Científica e de Ética da
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CERTIFICADO

Certificamos que o Protocolo para uso de animais em experimentação nº 092/03, sobre o projeto intitulado **"Efeitos da solução de Carnoy no reparo ósseo em cavidades experimentais de tíbias de ratos"**, sob a responsabilidade de **João Gualberto de Cerqueira Luz,** está de acordo com os Princípios Éticos na Experimentação Animal adotado pelo Colégio Brasileiro de Experimentação Animal (COBEA) e foi aprovado pela COMISSÃO DE ÉTICA EM EXPERIMENTAÇÃO ANIMAL (CEEA) em reunião de **13/10/2003.**

(We certify that the protocol nº **092/03,** about ***"Effect of Carnoy's solution on bone healing in experimental cavities in rat's tibia"*** agrees with the ETHICAL PRINCIPLES IN ANIMAL RESEARCH adopted by Brazilian College of Animal Experimentation (COBEA) and was approved by the BIOMEDICAL SCIENCES INSTITUTE/USP- ETHICAL COMMITTEE FOR ANIMAL RESEARCH (CEEA) in **13/10/2003** meeting.)

São Paulo, 15 de outubro de 2003.

Profa. Dra. Sonia Malheiros L. Sanioto
Coordenadora da CEEA

Profa. Dra. Marília Cerqueira Leite Seelaender
Secretária da CEEA

Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication

Updated October 2008

Publication Ethics: Sponsorship, Authorship, and Accountability

The following information is available to be viewed/printed in Adobe Acrobat pdf format.

International Committee of Medical Journal Editors

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I. Statement Of Purpose

I. A. About the Uniform Requirements

A small group of editors of general medical journals met informally in Vancouver, British Columbia, in 1978 to establish guidelines for the format of manuscripts submitted to their journals. This group became known as the Vancouver Group. Its requirements for manuscripts, including formats for bibliographic references developed by the National Library of Medicine (NLM), were first published in 1979. The Vancouver Group expanded and evolved into the International Committee of Medical Journal Editors (ICMJE), which meets annually. The ICMJE has gradually broadened its concerns to include ethical principles related to publication in biomedical journals.

The ICJME has produced multiple editions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Over the years, issues have arisen that go beyond manuscript preparation, resulting in the development of a number of Separate Statements on editorial policy. The entire Uniform Requirements document was revised in 1997; sections were updated in May 1999 and May 2000. In May 2001, the ICMJE revised the sections related to potential conflict of interest. In 2003, the committee revised and reorganized the entire document and incorporated the Separate Statements into the text. The

committee prepared this revision in 2008.

The total content of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals may be reproduced for educational, not-for-profit purposes without regard for copyright; the committee encourages distribution of the material.

Journals that agree to use the Uniform Requirements are encouraged to state in their instructions to authors that their requirements are in accordance with the Uniform Requirements and to cite this version. Journals that wish to be listed on www.ICMJE.org as a publication that follows the Uniform Requirements should contact the ICMJE secretariat office.

The ICMJE is a small working group of general medical journals, not an open-membership organization. Occasionally, the ICMJE will invite a new member or guest when the committee feels that the journal or organization will provide a new perspective. Open membership organizations for editors and others in biomedical publication include the World Association of Medical Editors www.WAME.org and the Council of Science Editors www.councilofscienceeditors.

I.B. Potential Users of the Uniform Requirements

The ICMJE created the Uniform Requirements primarily to help authors and editors in their mutual task of creating and distributing accurate, clear, easily accessible reports of biomedical studies. The initial sections address the ethical principles related to the process of evaluating, improving, and publishing manuscripts in biomedical journals and the relationships among editors and authors, peer reviewers, and the media. The latter sections address the more technical aspects of preparing and submitting manuscripts. The ICMJE believes that the entire document is relevant to the concerns of both authors and editors.

The Uniform Requirements can provide many other stakeholders—peer reviewers, publishers, the media, patients and their families, and general readers—with useful insights into the biomedical authoring and editing process.

I. C. How to Use the Uniform Requirements

The Uniform Requirements state the ethical principles in the conduct and reporting of research and provide recommendations relating to specific elements of editing and writing. These

recommendations are based largely on the shared experience of a moderate number of editors and authors, collected over many years, rather than on the results of methodical, planned investigation that aspires to be "evidence-based." Wherever possible, recommendations are accompanied by a rationale that justifies them; as such, the document serves an educational purpose.

Authors will find it helpful to follow the recommendations in this document whenever possible because, as described in the explanations, doing so improves the quality and clarity of reporting in manuscripts submitted to any journal, as well as the ease of editing. At the same time, every journal has editorial requirements uniquely suited to its purposes. Authors therefore need to become familiar with the Instructions to Authors specific to the journal they have chosen for their manuscript—for example, the topics suitable for that journal, and the types of papers that may be submitted (for example, original articles, reviews, or case reports)—and should follow those instructions.

II. Ethical Considerations in the Conduct and Reporting of Research

II.A Authorship and Contributorship

II.A.1. Byline Authors

An "author" is generally considered to be someone who has made substantive intellectual contributions to a published study, and biomedical authorship continues to have important academic, social, and financial implications (1). In the past, readers were rarely provided with information about contributions to studies from persons listed as authors and in Acknowledgments (2). Some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy, as well as a policy on identifying who is responsible for the integrity of the work as a whole.

While contributorship and guarantorship policies obviously remove much of the ambiguity surrounding contributions, they leave unresolved the question of the quantity and quality of contribution that qualify for authorship. The ICJME has recommended the following criteria for authorship; these criteria are still appropriate for journals that distinguish authors from

other contributors.

- Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript (3). These individuals should fully meet the criteria for authorship/contributorship defined above and editors will ask these individuals to complete journal-specific author and conflict-of-interest disclosure forms. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. The NLM indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript; it also lists the names of collaborators if they are listed in Acknowledgments.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Some journals now also request that one or more authors, referred to as “guarantors,” be identified as the persons who take responsibility for the integrity of the work as a whole, from inception to published article, and publish that information.

Increasingly, authorship of multicenter trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship/contributorship.

The group should jointly make decisions about contributors/authors before submitting the manuscript for publication. The corresponding author/guarantor should be prepared to explain the presence and order of these individuals. It

is not the role of editors to make authorship/contributorship decisions or to arbitrate conflicts related to authorship.

II.A.2. Contributors Listed in Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Editors should ask corresponding authors to declare whether they had assistance with study design, data collection, data analysis, or manuscript preparation. If such assistance was available, the authors should disclose the identity of the individuals who provided this assistance and the entity that supported it in the published article. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under such headings as “clinical investigators” or “participating investigators,” and their function or contribution should be described—for example, “served as scientific advisors,” “critically reviewed the study proposal,” “collected data,” or “provided and cared for study patients.” Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged.

II.B Editorship

II.B.1. The Role of the Editor

The editor of a journal is the person responsible for its entire content. Owners and editors of medical journals have a common endeavor—publication of a reliable, readable journal produced with due respect for the stated aims of the journal and for costs. Owners and editors, however, have different functions. Owners have the right to appoint and dismiss editors and to make important business decisions in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. The concept of editorial freedom should be resolutely defended by editors even to the extent of their placing their positions at stake. To secure this freedom in practice, the editor should have direct access to the highest level of ownership, not to a delegated manager.

Editors of medical journals should have a contract that clearly

states his or her rights and duties, the general terms of the appointment, and the mechanisms for resolving conflict.

An independent editorial advisory board may be useful in helping the editor establish and maintain editorial policy.

II.B.2. Editorial Freedom

The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom. According to this definition, editorial freedom, or independence, is the concept that editors-in-chief have full authority over the editorial content of their journal and the timing of publication of that content. Journal owners should not interfere in the evaluation, selection, or editing of individual articles either directly or by creating an environment that strongly influences decisions. Editors should base decisions on the validity of the work and its importance to the journal's readers not on the commercial success of the journal. Editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views conflict with the commercial goals of the publisher. Editors and editors' organizations have the obligation to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

II.C. Peer Review

Unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including the scientific process. Peer review is the critical assessment of manuscripts submitted to journals by experts who are not part of the editorial staff. Peer review can therefore be viewed as an important extension of the scientific process. Although its actual value has been little studied and is widely debated (4), peer review helps editors decide which manuscripts are suitable for their journals and helps authors and editors to improve the quality of reporting. A peer-reviewed journal submits most of its published research articles for outside review. The number and kinds of manuscripts sent for review, the number of reviewers, the reviewing procedures, and the use made of the reviewers' opinions may vary. In the interests of transparency, each journal should publicly disclose its policies in its Instructions to Authors.

II.D. Conflicts of Interest

Public trust in the peer-review process and the credibility of

published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from negligible to great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships (such as employment, consultancies, stock ownership, honoraria, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

All participants in the peer-review and publication process must disclose all relationships that could be viewed as potential conflicts of interest. Disclosure of such relationships is also important in connection with editorials and review articles, because it can be more difficult to detect bias in these types of publications than in reports of original research. Editors may use information disclosed in conflict-of-interest and financial-interest statements as a basis for editorial decisions. Editors should publish this information if they believe it is important in judging the manuscript.

II.D.1. Potential Conflicts of Interest Related to Individual Authors' Commitments

When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page, providing additional detail, if necessary, in a cover letter that accompanies the manuscript. *(See Section IV. A. 3. Conflict-of-Interest Notification Page)*

Authors should identify Individuals who provide writing or other assistance and disclose the funding source for this assistance.

Investigators must disclose potential conflicts to study

participants and should state in the manuscript whether they have done so.

Editors also need to decide whether to publish information disclosed by authors about potential conflicts. If doubt exists, it is best to err on the side of publication.

II.D.2. Potential Conflicts of Interest Related to Project Support

Increasingly, individual studies receive funding from commercial firms, private foundations, and government. The conditions of this funding have the potential to bias and otherwise discredit the research.

Scientists have an ethical obligation to submit creditable research results for publication. Moreover, as the persons directly responsible for their work, researchers should not enter into agreements that interfere with their access to the data and their ability to analyze them independently, and to prepare and publish manuscripts. Authors should describe the role of the study sponsor, if any, in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. If the supporting source had no such involvement, the authors should so state. Biases potentially introduced when sponsors are directly involved in research are analogous to methodological biases. Some journals, therefore, choose to include information in the Methods section about the sponsor's involvement.

Editors may request that authors of a study funded by an agency with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis." Editors should be encouraged to review copies of the protocol and/or contracts associated with project-specific studies before accepting such studies for publication. Editors may choose not to consider an article if a sponsor has asserted control over the authors' right to publish.

II.D.3. Potential Conflicts of Interest Related to Commitments of Editors, Journal Staff, or Reviewers

Editors should avoid selecting external peer reviewers with obvious potential conflicts of interest--for example, those who work in the same department or institution as any of the authors.

Authors often provide editors with the names of persons they feel should not be asked to review a manuscript because of potential, usually professional, conflicts of interest. When possible, authors should be asked to explain or justify their concerns; that information is important to editors in deciding whether to honor such requests.

Reviewers must disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and they should recuse themselves from reviewing specific manuscripts if the potential for bias exists. As in the case of authors, silence on the part of reviewers concerning potential conflicts may mean either that conflicts exist and the reviewer has failed to disclose them or conflicts do not exist. Reviewers must therefore also be asked to state explicitly whether conflicts do or do not exist. Reviewers must not use knowledge of the work, before its publication, to further their own interests.

Editors who make final decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues they might judge. Other members of the editorial staff, if they participate in editorial decisions, must provide editors with a current description of their financial interests (as they might relate to editorial judgments) and recuse themselves from any decisions in which a conflict of interest exists. Editorial staff must not use information gained through working with manuscripts for private gain. Editors should publish regular disclosure statements about potential conflicts of interests related to the commitments of journal staff.

II.E. Privacy and Confidentiality

II. E.1. Patients and Study Participants

Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived either with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to

locale, and journals should establish their own policies with legal guidance.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance, and editors should so note, that such alterations do not distort scientific meaning.

The requirement for informed consent should be included in the journal's Instructions for Authors. When informed consent has been obtained, it should be indicated in the published article.

II.E.2. Authors and Reviewers

Manuscripts must be reviewed with due respect for authors' confidentiality. In submitting their manuscripts for review, authors entrust editors with the results of their scientific work and creative effort, on which their reputation and career may depend. Authors' rights may be violated by disclosure of the confidential details during review of their manuscript. Reviewers also have rights to confidentiality, which must be respected by the editor. Confidentiality may have to be breached if dishonesty or fraud is alleged but otherwise must be honored.

Editors must not disclose information about manuscripts (including their receipt, content, status in the reviewing process, criticism by reviewers, or ultimate fate) to anyone other than the authors and reviewers. This includes requests to use the materials for legal proceedings.

Editors must make clear to their reviewers that manuscripts sent for review are privileged communications and are the private property of the authors. Therefore, reviewers and members of the editorial staff must respect the authors' rights by not publicly discussing the authors' work or appropriating their ideas before the manuscript is published. Reviewers must not be allowed to make copies of the manuscript for their files and must be prohibited from sharing it with others, except with the editor's permission. Reviewers should return or destroy copies of manuscripts after submitting reviews. Editors should not keep copies of rejected manuscripts.

Reviewer comments should not be published or otherwise

publicized without permission of the reviewer, author, and editor.

Opinions differ on whether reviewers should remain anonymous. Authors should consult the Information for Authors of the journal to which they have chosen to submit a manuscript to determine whether reviews are anonymous. When comments are not signed, the reviewers' identity must not be revealed to the author or anyone else without the reviewers' permission.

Some journals publish reviewers' comments with the manuscript. No such procedure should be adopted without the consent of the authors and reviewers. However, reviewers' comments should be sent to other persons reviewing the same manuscript, which helps reviewers learn from the review process. Reviewers also may be notified of the editor's decision to accept or reject a manuscript.

II.F. Protection of Human Subjects and Animals in Research

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

III. Publishing and Editorial Issues Related to Publication in Biomedical Journals

III.A. Obligation to Publish Negative Studies

Editors should consider seriously for publication any carefully done study of an important question, relevant to their readers, whether the results for the primary or any additional outcome are statistically significant. Failure to submit or publish findings because of lack of statistical significance is an important cause of publication bias.

III.B. Corrections, Retractions and "Expressions of Concern"

Editors must assume initially that authors are reporting work based on honest observations. Nevertheless, two types of difficulty may arise.

First, errors may be noted in published articles that require the publication of a correction or erratum on part of the work. The corrections should appear on a numbered page, be listed in the Table of Contents, include the complete original citation, and link to the original article and vice versa if online. It is conceivable that an error could be so serious as to vitiate the entire body of the work, but this is unlikely and should be addressed by editors and authors on an individual basis. Such an error should not be confused with inadequacies exposed by the emergence of new scientific information in the normal course of research. The latter requires no corrections or withdrawals.

The second type of difficulty is scientific fraud. If substantial doubts arise about the honesty or integrity of work, either submitted or published, it is the editor's responsibility to ensure that the question is appropriately pursued, usually by the authors' sponsoring institution. Ordinarily it is not the responsibility of the editor to conduct a full investigation or to make a determination; that responsibility lies with the institution where the work was done or with the funding agency. The editor should be promptly informed of the final decision, and if a fraudulent paper has been published, the journal must print a retraction. If this method of investigation does not result in a satisfactory conclusion, the editor may choose to conduct his or her own investigation. As an alternative to retraction, the editor may choose to publish an expression of concern about aspects of the conduct or integrity of the work.

The retraction or expression of concern, so labeled, should appear on a numbered page in a prominent section of the print journal as well as in the online version, be listed in the Table of Contents page, and include in its heading the title of the original article. It should not simply be a letter to the editor. Ideally, the first author of the retraction should be the same as that of the article, although under certain circumstances the editor may accept retractions by other responsible persons. The text of the retraction should explain why the article is being retracted and include a complete citation reference to that article.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of earlier work published in their journals or to retract it. If this is not done, editors may choose to

publish an announcement expressing concern that the validity of previously published work is uncertain.

Editors who have questions related to editorial or scientific misconduct may find it useful to consult the excellent flow charts that the Committee on Publication Ethics (COPE) has developed (http://www.publicationethics.org.uk). COPE, which was formed in 1997, is a forum in which editors of peer-reviewed journals can discuss issues related to the integrity of the scientific record; it supports and encourages editors to report, catalogue, and instigate investigations into ethical problems in the publication process. COPE's major objective is to provide a sounding board for editors struggling with how best to deal with possible breaches in research and publication ethics.

III.C. Copyright

Many biomedical journals ask authors to transfer copyright to the journal. However, an increasing number of "open-access" journals do not require transfer of copyright. Editors should make their position on copyright transfer clear to authors and to others who might be interested in using editorial content from their journals. The copyright status of articles in a given journal can vary: Some content cannot be copyrighted (for example, articles written by employees of the U.S. and some other governments in the course of their work); editors may agree to waive copyright on others; and still others may be protected under serial rights (that is, use in publications other than journals, including electronic publications, is permitted).

III.D. Overlapping Publications

III.D.1. Duplicate Submission

Most biomedical journals will not consider manuscripts that are simultaneously being considered by other journals. Among the principal considerations that have led to this policy are: 1) the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one; and 2) the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review, edit the same manuscript, and publish the same article.

However, editors of different journals may decide to simultaneously or jointly publish an article if they believe that

doing so would be in the best interest of public health.

III.D.2. Redundant Publication

Redundant (or duplicate) publication is publication of a paper that overlaps substantially with one already published in print or electronic media.

Readers of primary source periodicals, whether print or electronic, deserve to be able to trust that what they are reading is original unless there is a clear statement that the author and editor are intentionally republishing an article. The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic, since it can result in inadvertent double counting or inappropriate weighting of the results of a single study, which distorts the available evidence.

Most journals do not wish to receive papers on work that has already been reported in large part in a published article or is contained in another paper that has been submitted or accepted for publication elsewhere, in print or in electronic media. This policy does not preclude the journal considering a paper that has been rejected by another journal, or a complete report that follows publication of a preliminary report, such as an abstract or poster displayed at a professional meeting. It also does not prevent journals from considering a paper that has been presented at a scientific meeting but was not published in full or that is being considered for publication in a proceedings or similar format. Press reports of scheduled meetings are not usually regarded as breaches of this rule, but additional data or copies of tables and illustrations should not amplify such reports. The ICMJE does not consider results posted in clinical trial registries as previous publication if the results are presented in the registry in the form of a brief structured abstract or table. The Results registry should either cite the full publication or include a statement that indicates that the report has not been published in a peer-reviewed journal.

When submitting a paper, the author must always make a complete statement to the editor about all submissions and previous reports (including meeting presentations and posting of results in registries) that might be regarded as redundant or duplicate publication. The author must alert the editor if the manuscript includes subjects about which the authors have published a previous report or have submitted a related report to another publication. Any such report must be referred to and

referenced in the new paper. Copies of such material should be included with the submitted manuscript to help the editor decide how to handle the matter.

If redundant or duplicate publication is attempted or occurs without such notification, authors should expect editorial action to be taken. At the least, prompt rejection of the submitted manuscript should be expected. If the editor was not aware of the violations and the article has already been published, then a notice of redundant or duplicate publication will probably be published with or without the author's explanation or approval.

Preliminary reporting to public media, governmental agencies, or manufacturers of scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances or public health hazards, such as serious adverse effects of drugs, vaccines, other biological products, or medicinal devices, or reportable diseases. This reporting should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance.

III.D.3. Acceptable Secondary Publication

Certain types of articles, such as guidelines produced by governmental agencies and professional organizations, may need to reach the widest possible audience. In such instances, editors sometimes deliberately publish material that is also being published in other journals, with the agreement of the authors and the editors of those journals. Secondary publication for various other reasons, in the same or another language, especially in other countries, is justifiable and can be beneficial provided that the following conditions are met.

1. The authors have received approval from the editors of both journals; the editor concerned with secondary publication must have a photocopy, reprint, or manuscript of the primary version.

2. The priority of the primary publication is respected by a publication interval of at least 1 week (unless specifically negotiated otherwise by both editors).

3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.

4. The secondary version faithfully reflects the data and

interpretations of the primary version.

5. The footnote on the title page of the secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part and states the primary reference. A suitable footnote might read: “This article is based on a study first reported in the [title of journal, with full reference].”

Permission for such secondary publication should be free of charge.

6. The title of the secondary publication should indicate that it is a secondary publication (complete republication, abridged republication, complete translation, or abridged translation) of a primary publication. Of note, the NLM does not consider translations to be “republications” and does not cite or index translations when the original article was published in a journal that is indexed in MEDLINE.

7. Editors of journals that simultaneously publish in multiple languages should understand that NLM indexes the primary language version. When the full text of an article appears in more than one language in a journal issue (such as Canadian journals with the article in both English and French), both languages are indicated in the MEDLINE citation (for example, Mercer K. The relentless challenge in health care. Healthc Manage Forum. 2008 Summer;21(2):4-5. English, French. No abstract available. PMID:18795553.)

III.D.4. Competing Manuscripts Based on the Same Study

Publication of manuscripts to air the disputes of co-investigators may waste journal space and confuse readers. On the other hand, if editors knowingly publish a manuscript written by only some of a collaborating team, they could be denying the rest of the team their legitimate co-authorship rights and journal readers access to legitimate differences of opinion about the interpretation of a study.

Two kinds of competing submissions are considered: submissions by coworkers who disagree on the analysis and interpretation of their study, and submissions by coworkers who disagree on what the facts are and which data should be reported.

Setting aside the unresolved question of ownership of the data, the following general observations may help editors and others

address such problems.

III. D.4.a. Differences in Analysis or Interpretation

If the dispute centers on the analysis or interpretation of data, the authors should submit a manuscript that clearly presents both versions. The difference of opinion should be explained in a cover letter. The normal process of peer and editorial review may help the authors to resolve their disagreement regarding analysis or interpretation.

If the dispute cannot be resolved and the study merits publication, both versions should be published. Options include publishing two papers on the same study, or a single paper with two analyses or interpretations. In such cases, it would be appropriate for the editor to publish a statement outlining the disagreement and the journal's involvement in attempts to resolve it.

III.D.4. b. Differences in Reported Methods or Results

If the dispute centers on differing opinions of what was actually done or observed during the study, the journal editor should refuse publication until the disagreement is resolved. Peer review cannot be expected to resolve such problems. If there are allegations of dishonesty or fraud, editors should inform the appropriate authorities; authors should be notified of an editor's intention to report a suspicion of research misconduct.

III.D.5. Competing Manuscripts Based on the Same Database

Editors sometimes receive manuscripts from separate research groups that have analyzed the same data set (for example, from a public database). The manuscripts may differ in their analytic methods, conclusions, or both. Each manuscript should be considered separately. If interpretation of the data is very similar, it is reasonable but not mandatory for editors to give preference to the manuscript that was received first. However, editorial consideration of multiple submissions may be justified under these circumstances, and there may even be a good reason to publish more than one manuscript because different analytical approaches may be complementary and equally valid.

III.E. Correspondence

The corresponding author/guarantor has primary responsibility for correspondence with the journal, but the ICMJE recommends

that editors send a copy of any correspondence to all listed authors.

Biomedical journals should provide the readership with a mechanism for submitting comments, questions, or criticisms about published articles, as well as brief reports and commentary unrelated to previously published articles. This probably but not necessarily takes the form of a correspondence section or column. The authors of articles discussed in correspondence should be given an opportunity to respond, preferably in the same issue in which the original correspondence appears. Authors of correspondence should be asked to declare any competing or conflicting interests.

Published correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to publish unedited correspondence, for example in rapid-response sections on the Internet. The journal should declare its editorial practices in this regard. Authors should approve editorial changes that alter the substance or tone of a letter or response. In all instances, editors must make an effort to screen out discourteous, inaccurate, or libelous statements and should not allow ad hominem arguments intended to discredit opinions or findings.

Although editors have the prerogative to reject correspondence that is irrelevant, uninteresting, or lacking cogency, they have a responsibility to allow a range of opinions to be expressed. The correspondence column should not be used merely to promote the journal's or the editors' point of view.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to published material and for debate on a given topic. Journals should also decide whether they would notify authors when correspondence bearing on their published work is going to appear in standard or rapid-response sections. Journals should also set policy with regard to the archiving of unedited correspondence that appears online. These policies should be published both in print and electronic versions of the journal.

III.F. Supplements, Theme Issues, and Special Series

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and are usually funded by sources other than the journal's publisher. Supplements can serve useful

purposes: education, exchange of research information, ease of access to focused content, and improved cooperation between academic and corporate entities. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should consider adopting the following principles. These same principles apply to theme issues or special series that have external funding and/or guest editors.

1. The journal editor must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to publish all portions of the supplement. Editing by the funding organization should not be permitted.
2. The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement. These conditions should be made known to authors and external supplement editors before beginning editorial work on the supplement.
3. The journal editor must approve the appointment of any external editor of the supplement and take responsibility for the work of the external editor.
4. The sources of funding for the research, publication, and products of the funding source that are considered in the supplement should be clearly stated and prominently located in the supplement, preferably on each page. Whenever possible, supplements should be funded by more than one sponsor.
5. Advertising in supplements should follow the same policies as those of the rest of the journal.
6. Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.
7. Journal editors and supplement editors must not accept personal favors or remuneration from sponsors of supplements.
8. Secondary publication in supplements (republication of papers published elsewhere) should be clearly identified by the citation of the original paper. Supplements should avoid redundant or duplicate publication. Supplements should not republish research results, but republication of guidelines or other material in the public interest might be appropriate.
9. The principles of authorship and disclosure of potential conflicts of interest discussed elsewhere in this document should be applied to supplements.

III.G. Electronic Publishing

Most biomedical journals are now published in electronic as well as print versions, and some are published only in electronic form. Because electronic publishing (which includes the Internet) is the same as publishing in print, in the interests of clarity and consistency the recommendations of this document should be applied to electronically published medical and health information.

The nature of electronic publication requires some special considerations, both within and beyond this document. At a minimum, Web sites should indicate the following: names, appropriate credentials, affiliations, and relevant conflicts of interest of editors, authors, and contributors; documentation and attribution of references and sources for all content; information about copyright; disclosure of site ownership; and disclosure of sponsorship, advertising, and commercial funding.

Linking from one health or medical Internet site to another may be perceived as an implicit recommendation of the quality of the second site. Journals thus should exercise caution in linking to other sites; when users are linking to another site, it may be helpful to provide an explicit statement that they are leaving the journal's site. Links to other sites posted as a result of financial considerations should be clearly indicated as such. All dates of content posting and updating should be indicated. In electronic layout as in print, advertising and promotional messages should not be juxtaposed with editorial content, and commercial content should be clearly identified as such.

Electronic publication is in flux. Editors should develop, make available to authors, and implement policies on issues unique to electronic publishing. These issues include archiving, error correction, version control, choice of the electronic or print version of the journal as the journal of record, and publication of ancillary material.

Under no circumstances should a journal remove an article from its Web site or archive. If a correction or retraction becomes necessary, the explanation must be labeled appropriately and communicated as soon as possible on a citable page in a subsequent issue of the journal.

Preservation of electronic articles in a permanent archive is essential for the historical record. Access to the archive should be immediate and should be controlled by a third party, such as a

library, instead of the publisher. Deposition in multiple archives is encouraged.

III.H. Advertising

Most medical journals carry advertising, which generates income for their publishers, but advertising must not be allowed to influence editorial decisions. Journals should have formal, explicit, written policies for advertising in both print and electronic versions; Web site advertising policy should parallel that for the print version to the extent possible. Editors must have full and final authority for approving advertisements and enforcing advertising policy.

When possible, editors should make use of the judgments of independent bodies for reviewing advertising. Readers should be able to distinguish readily between advertising and editorial material. The juxtaposition of editorial and advertising material on the same products or subjects should be avoided. Interleafing advertising pages within articles interrupts the flow of editorial content and should be discouraged. Advertising should not be sold on the condition that it will appear in the same issue as a particular article.

Journals should not be dominated by advertising, but editors should be careful about publishing advertisements from only one or two advertisers, as readers may perceive that these advertisers have influenced the editor.

Journals should not carry advertisements for products that have proved to be seriously harmful to health—for example, tobacco. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other nondisplay advertising, except where required by law. Finally, editors should consider all criticisms of advertisements for publication.

III. I. Medical Journals and the General Media

The public’s interest in news of medical research has led the popular media to compete vigorously for information about research. Researchers and institutions sometimes encourage reporting research in the nonmedical media before full publication in a scientific journal by holding a press conference

or giving interviews.

The public is entitled to important medical information within a reasonable amount of time, and editors have a responsibility to facilitate the process. Biomedical journals are published primarily for their readers, but the general public has a legitimate interest in their content: An appropriate balance between these considerations should guide the journal's interaction with the media. Doctors in practice need to have reports available in full detail before they can advise their patients about the reports' conclusions. Moreover, media reports of scientific research before the work has been peer reviewed and fully vetted may lead to dissemination of inaccurate or premature conclusions.

An embargo system has been established in some countries to prevent publication of stories in the general media before publication of the original research in the journal. The embargo creates a "level playing field," which most reporters appreciate since it minimizes the pressure on them to publish stories which they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has great potential to influence financial markets. On the other hand, the embargo system has been challenged as being self-serving of journals' interests and an impediment to rapid dissemination of scientific information.

Editors may find the following recommendations useful as they seek to establish policies on these issues.

- Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication of the original research in the journal, in return for which the journal will cooperate with them in preparing accurate stories.
- Editors need to keep in mind that an embargo system works on the honor system; no formal enforcement or policing mechanism exists. The decision of a significant number of media outlets or biomedical journals not to respect the embargo system would lead to its rapid dissolution.
- Very little medical research has such clear and urgently

important clinical implications for the public's health that the news must be released before full publication in a journal. However, if such exceptional circumstances occur, the appropriate authorities responsible for public health should decide whether to disseminate information to physicians and the media in advance and should be responsible for this decision. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors acknowledge the need for immediate release, they should waive their policies limiting prepublication publicity.

- Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Redundant Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters, but they should be discouraged from offering more detail about their study than was presented in the talk.
- When an article is soon to be published, editors should help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the journal, or referring reporters to the appropriate experts. This assistance should be contingent on the media's cooperation in timing the release of a story to coincide with publication of the article.
- Editors, authors, and the media should apply the above-stated principles to material released early in electronic versions of journals.

III.J. Obligation to Register Clinical Trials

The ICMJE believes that it is important to foster a comprehensive, publicly available database of clinical trials. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

The ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry. The details of this policy are contained in a series of editorials (see editorials, under Frequently Asked

Questions). The ICMJE encourages editors of other biomedical journals to adopt similar policy.

The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the data elements listed in Table 1. Trial registration with missing fields or fields that contain uninformative terminology is inadequate.

It is important to note that the ICMJE requires registration of trial methodology but does not require registration of trial results; it recognizes the potential problems that could arise from the posting of research results that have not been subjected to an independent peer-review process. However, the ICMJE understands that the U.S. Food and Drug Administration Amendments Act of 2007 (FDAAA) does require researchers to register results. The ICMJE will not consider to be previous publication results posted in the same primary clinical trial registry as the initial registration if the results are posted in the tabular form dictated by the FDAAA. Researchers should be aware that editors of journals that follow the ICMJE recommendations may consider more detailed description of trial results and results published in registries other than the primary registry (in the case of FDAAA, ClinicalTrials.gov) to be prior publication. The ICMJE anticipates that the climate for results registration will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results registration.

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list the registration number the first time they use a trial acronym to refer to either the trial they are reporting or to other trials that they mention in the manuscript.

IV. Manuscript Preparation and Submission

IV.A. Preparing a Manuscript for Submission to a Biomedical Journal

Editors and reviewers spend many hours reading manuscripts, and therefore appreciate receiving manuscripts that are easy to read and edit. Much of the information in a journal's Instructions to Authors is designed to accomplish that goal in ways that meet each journal's particular editorial needs. The following information provides guidance in preparing manuscripts for any journal.

IV.A.1.a. General Principles

The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is not an arbitrary publication format but rather a direct reflection of the process of scientific discovery. Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently.

Electronic formats have created opportunities for adding details or whole sections, layering information, cross-linking or extracting portions of articles, and the like only in the electronic version. Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.

Double spacing all portions of the manuscript— including the title page, abstract, text, acknowledgments, references, individual tables, and legends—and generous margins make it possible for editors and reviewers to edit the text line by line and add comments and queries directly on the paper copy. If manuscripts are submitted electronically, the files should be double-spaced to facilitate printing for reviewing and editing.

Authors should number all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

IV.A.1.b. Reporting Guidelines for Specific Study Designs

Research reports frequently omit important information. Reporting guidelines (Table 2) have been developed for a number of study designs that some journals may ask authors to follow. Authors should consult the Information for Authors of the journal they have chosen.

The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged also to consult reporting guidelines relevant to their specific research design. For reports of randomized, controlled trials, authors should refer to the CONSORT statement. This guideline provides a set of recommendations comprising a list of items to report and a patient flow diagram.

IV.A.2. Title Page

The title page should carry the following information:

1. Article title. Concise titles are easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying randomized, controlled trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
2. Authors' names and institutional affiliations. Some journals publish each author's highest academic degree(s), while others do not.
3. The name of the department(s) and institution(s) to which the work should be attributed.
4. Disclaimers, if any.
5. Contact information for corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript (the "corresponding author;" this author may or may not be the "guarantor" for the integrity of the study). The corresponding author should indicate clearly whether his or her e-mail address can be published.
6. The name and address of the author to whom requests for reprints should be addressed or a statement that reprints are not available from the authors.
7. Source(s) of support in the form of grants, equipment, drugs, or all of these.
8. A running head. Some journals request a short running head or footline, usually no more than 40 characters (including letters and spaces) at the foot of the title page. Running heads are published in most journals, but are also sometimes used within the editorial office for filing and locating manuscripts.
9. Word counts. A word count for the text only (excluding abstract, acknowledgments, figure legends, and references) allows editors and reviewers to assess

whether the information contained in the paper warrants the amount of space devoted to it, and whether the submitted manuscript fits within the journal's word limits. A separate word count for the Abstract is useful for the same reason.

10. The number of figures and tables. It is difficult for editorial staff and reviewers to determine whether the figures and tables that should have accompanied a manuscript were actually included unless the numbers of figures and tables are noted on the title page.

IV.A.3. Conflict of Interest Notification Page

To prevent the information on potential conflicts of interest from being overlooked or misplaced, it needs to be part of the manuscript. However, it should also be included on a separate page or pages immediately following the title page. Individual journals may differ in where they include this information, and some journals do not send information on conflicts of interest to reviewers. (***See Section II. D. Conflicts of Interest***.)

IV.A.4. Abstract

The abstract (requirements for length and format vary) should follow the title page. It should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations. Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (http://www.consort-statement.org/?=1190).

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that they accurately reflect the content of the article. Unfortunately, the information contained in many abstracts differs from that in the text (6). The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also

recommends that, whenever a registration number is available, authors list that number the first time they use a trial acronym to refer to either the trial they are reporting or to other trials that they mention in the manuscript.

IV.A.5. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be clear, and any prespecified subgroup analyses should be described. Provide only directly pertinent references, and do not include data or conclusions from the work being reported.

IV.A.6. Methods

The Methods section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section.

IV.A.6.a. Selection and Description of Participants

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report--for example, authors should explain why only participants of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use such variables as race or ethnicity, they should define how they measured these variables and justify their relevance.

IV.A.6.b. Technical information

Identify the methods, apparatus (give the manufacturer’s name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or

substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

IV.A.6.c. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

IV.A.7. Results

Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.”

Where scientifically appropriate, analyses of the data by such variables as age and sex should be included.

IV.A.8. Discussion

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other information given in the Introduction or the Results section. For experimental studies, it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly as such.

IV.A.9. References

IV.A.9.a. General Considerations Related to References

Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as “in press” or “forthcoming”; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as “unpublished observations” with written permission from the

source.

Avoid citing a “personal communication” unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, verify references against the original documents. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by using the following search term, where pt in square brackets stands for publication type: Retracted publication [pt] in PubMed.

IV.A.9.b. Reference Style and Format

The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the NLM for its databases. Authors should consult NLM’s Citing Medicine for information on its recommended formats for a variety of reference types.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in the list of Journals Indexed for MEDLINE, posted by the NLM on the Library's web site. Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

IV.A.10. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently

makes it possible to reduce the length of the text.

Type or print each table with double spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use the following symbols, in sequence:

*,†,‡,§,||,¶,**,††,‡‡

Identify statistical measures of variations, such as standard deviation and standard error of the mean.

Be sure that each table is cited in the text.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

IV.A.11. Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. In addition to requiring a version of the figures suitable for printing, some journals now ask authors for electronic files of figures in a format (for example, JPEG or GIF) that will produce high-quality images in the Web version of the journal; authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards.

For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 x 173 mm (5 x 7 inches). Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and

large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends--not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background.

Photographs of potentially identifiable people must be accompanied by written permission to use the photograph.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure. Permission is required irrespective of authorship or publisher except for documents in the public domain.

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. Some journals publish illustrations in color only if the author pays the additional cost.

Authors should consult the journal about requirements for figures submitted in electronic formats.

IV.A.12. Legends for Illustrations (Figures)

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

IV.A.13. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are

specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI). Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

IV.A.14. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

IV.B Sending the Manuscript to the Journal

An increasing number of journals now accept electronic submission of manuscripts, whether on disk, as an e-mail attachment, or by downloading directly onto the journal's Web site. Electronic submission saves time and money and allows the manuscript to be handled in electronic form throughout the editorial process (for example, when it is sent out for review). For specific instructions on electronic submission, authors should consult the journal's Instructions for Authors.

If a paper version of the manuscript is submitted, send the required number of copies of the manuscript and figures; they are all needed for peer review and editing, and the editorial office staff cannot be expected to make the required copies.

Manuscripts must be accompanied by a cover letter, which should include the following information.

- A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor address the situation.

- A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form.
- A statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work if that information is not provided in another form (see below).
- The name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs, if that information is not included in the manuscript itself.

The letter should give any additional information that may be helpful to the editor, such as the type or format of article in the particular journal that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Editors encourage authors to submit these previous communications. Doing so may expedite the review process.

Many journals now provide a presubmission checklist to help the author ensure that all the components of the submission have been included. Some journals now also require that authors complete checklists for reports of certain study types (for example, the CONSORT checklist for reports of randomized, controlled trials). Authors should look to see if the journal uses such checklists, and send them with the manuscript if they are requested.

Letters of permission to reproduce previously published material, use previously published illustrations, report information about identifiable persons, or to acknowledge people for their contributions must accompany the manuscript.

V. References

A. References Cited in this Document

1. Davidoff F, for the CSE Task Force on Authorship. Who's the author? Problems with biomedical authorship, and some possible solutions. Science Editor. 2000 ;23:111-9.

2. Yank V, Rennie D. Disclosure of researcher contributions: a study of original research articles in The Lancet. Ann Intern Med. 1999;130:661-70.

3. Flanagin A, Fontanarosa PB, DeAngelis CD. Authorship for research groups. JAMA. 2002;288:3166-8.

4. Godlee F, Jefferson T. Peer Review in Health Sciences. London: BMJ Books; 1999.

5. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA. 2000;284:3043-5.

6. Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. JAMA. 1999;281:1110-1.

B. Other Sources of Information Related to Biomedical Journals

World Association of Medical Editors (WAME)

Council of Science Editors (CSE)

European Association of Science Editors (EASE)

Cochrane Collaboration

Committee on Publication Ethics

VI. About The International Committee of Medical Journal Editors

The ICMJE is a group of general medical journal editors whose participants meet annually and fund their work on the Uniform Requirements for Manuscripts. The ICMJE invites comments on this document and suggestions for agenda items.

VII. Authors of The Uniform Requirements for Manuscripts Submitted to Biomedical Journals

The ICMJE participating journals and organizations and their representatives who approved the revised Uniform Requirements for Manuscripts in September 2008 include *Annals of Internal Medicine, British Medical Journal, Canadian Medical Association Journal, Croatian Medical Journal, Journal of the*

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Revista Brasileira de OTORRINO LARINGOLOGIA

ISSN 0034-7299 *versão impressa*
ISSN 1806-9312 *versão on-line*

INSTRUÇÕES AOS AUTORES

Escopo e política

A política editorial da Revista Brasileira de Otorrinolaringologia é voltada para a divulgação de trabalhos científicos de grande interesse da especialidade e de suas áreas de atuação, procurando privilegiar os trabalhos originais (sobretudo os ensaios clínicos e os estudos experimentais) e para dar vazão às pesquisas feitas no âmbito dos cursos de pós-graduação da área, obedecendo a ordem de submissão dos manuscritos. Relatos de caso que sejam de forte impacto para o conhecimento científico, bem como artigos de revisão também têm seus espaços. Além disso, cada fascículo contém um editorial que procura discutir temas de interesse científico, acadêmico ou profissional da especialidade.

Todos os trabalhos submetidos são avaliados por dois ou mais revisores otorrinolaringologistas de reconhecida atividade científica em instituições públicas ou privadas ligadas ao ensino da otorrinolaringologia em programas de pós-graduação.

A revista é dirigida a um público basicamente de otorrinolaringologistas de todo o mundo, visto que possui uma versão em inglês indexada, mas também aos profissionais de atividades correlatas (fonoaudiólogos, odontólogos, cirurgiões de cabeça e pescoço, cirurgiões plásticos, pediatras entre outros).

A Revista Brasileira de Otorrinolaringologia apóia as políticas para registro de ensaios clínicos da Organização Mundial de Saúde (OMS) e do International Committee of Medical Journal Editors (ICMJE), reconhecendo a importância dessas iniciativas para o registro e divulgação internacional de informação sobre estudos clínicos, em acesso aberto. Sendo

assim, somente são aceitos para publicação os artigos de pesquisas clínicas que tenham recebido um número de identificação em um dos Registros de Ensaios Clínicos validados pelos critérios estabelecidos pela OMS e ICMJE, cujos endereços estão disponíveis no site do ICMJE. O número de identificação deve ser registrado ao final do resumo.

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Na **Introdução** é onde estão a revisão da literatura, as premissas teóricas , a justificativa e o objetivo do trabalho.

No **Material e Método** espera -se encontrar a descrição da amostra estudada e um detalhamento suficiente do instrumento de investigação.

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INTERNATIONAL JOURNAL OF SURGERY

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By Riaz Agha | Published Friday 15 September 2006

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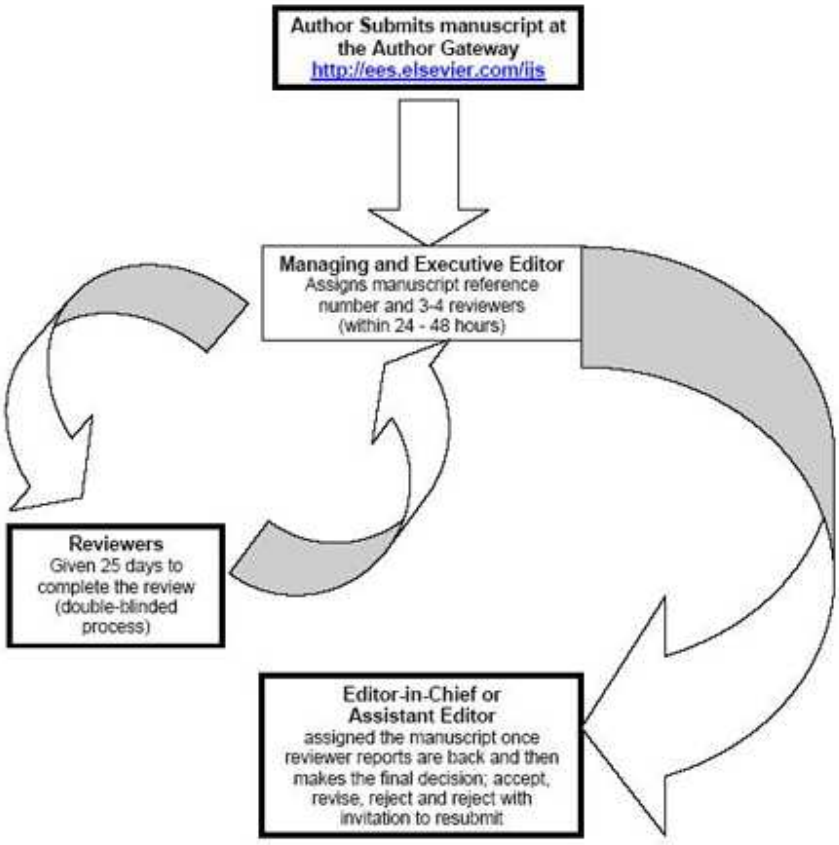

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