PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIAS DA SAÚDE

HENRIQUE BARRETO BELLUSCI

AÇÃO ANTIMICROBIANA DOS ANESTÉSICOS LOCAIS EM RELAÇÃO A *Staphylococcus* spp.: REVISÃO SISTEMÁTICA

Presidente Prudente - SP
2022

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Dissertação apresentada à Pró-Reitoria de Pesquisa e Pós-Graduação, Universidade do Oeste Paulista, como parte dos requisitos para obtenção do título de Mestre em Ciências da Saúde. – Área de concentração: Ciências da Saúde.

Orientador:
Profa. Dra. Lizziane Kretli Winkelströter Eller

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Presidente Prudente, 6 de setembro de 2022

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Uma dissertação de Mestrado surge da combinação de esforços de uma equipe. Desde a escolha do tema, metodologia até chegarmos nos resultados foi uma caminhada com obstáculos que fomos superando com a dedicação de todos.

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Agradeço à Deus e minha família por ser meu alicerce e busca de inspiração pra chegar até o final dessa jornada.

RESUMO

Ação antimicrobiana dos anestésicos locais em relação a *Staphylococcus* spp.: revisão sistemática

É relatado que agentes anestésicos podem limitar o crescimento de microrganismos como por exemplo *Staphylococcus* spp.. O objetivo desse trabalho foi realizar uma revisão sistemática sobre a eficácia de anestésicos locais como agente antimicrobiano contra *Staphylococcus* spp. As buscas foram realizadas nas bases de dados Pubmed, Web of science, Scopus, Embase e Lilacs. Foram selecionados artigos originais completos, ensaios experimentais in vitro com aplicação dos anestésicos selecionados e bactéria do gênero *Staphylococcus* spp. A presente revisão seguiu ao checklist metodológico para a redação de trabalhos reportando revisões sistemáticas pela declaração Prisma. Foi avaliado o risco de viés de acordo com JBI critical appraisal checklist quase experimental versão adaptada. Foi realizado análise por um modelo de regressão linear simples moderado por anestésico. Essa revisão sistemática foi registrada pela Open Science Framework-OSF (DOI 10.17605/OSF.IO/C5JM7). Inicialmente foram encontrados 1141 artigos, entretanto, foram analisados 52 artigos após seleção criteriosa. A lidocaína foi o anestésico mais aplicado, sendo avaliado em 35 dos artigos. *S. aureus* ATCC 25923 foi o microrganismo padrão em 17 artigos. Foi avaliado o impacto da concentração do anestésico em relação ao efeito antimicrobiano e os resultados demonstraram que não houve diferença estatisticamente significativa ($F [5, 12] = 0,688$ $p = 0,642$), mesmo quando levado em consideração o efeito moderado pelos anestésicos individualmente. Diante disso, apesar de ter sido demonstrado o efeito antimicrobiano dos anestésicos locais em 82,7% dos estudos avaliados foi encontrado uma grande heterogeneidade dos resultados o que impossibilitou a realização de meta-nálise e futuras recomendações baseadas em evidências.

Palavras-chave: Lidocaína, antimicrobiano, bactericida

ABSTRACT

Antimicrobial action of local anesthetics in relation to *Staphylococcus* spp.:sustematic review

It is reported that anesthetic agents can limit the growth of microorganisms such as *Staphylococcus* spp. The objective of this work was to conduct a systematic review on the efficacy of local anesthetics as an antimicrobial agent against *Staphylococcus* spp. The searches were carried out in the databases Pubmed, Web of science, Scopus, Embase and Lilacs. As inclusion criteria, complete original articles, experimental in vitro assays with application of selected anesthetics and bacteria of the genus *Staphylococcus* spp were selected. This review followed the methodological checklist for the writing of papers reporting systematic reviews by prisma statement. The risk of bias was assessed according to JBI critical appraisal checklist. Analysis was performed by a simple linear regression model moderated by anesthetic. This systematic review was recorded by the Open Science Framework - OSF (DOI 10.17605/OSF.IO/C5JM7). Initially, 1,141 articles were found, however, 52 articles were analyzed after careful selection. Lidocaine was the most applied anesthetic, being evaluated in 35 of the articles. *S. aureus* ATCC 25923 was the standard microorganism in 17 articles. The impact of anesthetic concentration in relation to antimicrobial effect was evaluated and the results showed that there was no statistically significant difference ($F [5, 12] = 0.688$ $p = 0.642$), even when considering the moderate effect by anesthetics individually. Therefore, despite the fact that the antimicrobial effect of local anesthetics was demonstrated in 82.7% of the studies evaluated, a great heterogeneity of the results was found, which made it impossible to perform meta-analysis and future evidence-based recommendations.

Keywords: Lidocaine, antimicrobial, bactericidal

LISTA DE SIGLAS

AgNPs – Nanopartículas de prata
AL – Anestésico Local
ATCC – American Type Culture Collection
CBM – Concentração Bactericida Mínima
CIM – Concentração Inibitória Mínima
CLSI – Clinical and Laboratory Standards Institute
DNA – Ácido Desoxirribonucleico
EMLA – Mistura Enantiomérica com Anestésicos Locais
IC – Índice de Confiança
HA – Ácido hialurônico
JBI – Joanna Briggs Institute
LID – Lidocaína
MRSA – Staphylococcus aureus resistente à meticilina
MSSA – Staphylococcus aureus sensível à meticilina
NIH – National Institutes of Health
OSF – Open Science Framework
RR – Risco Relativo
SLMPs – Solid lipid microparticles

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RESUMO

É relatado que agentes anestésicos podem limitar o crescimento de microrganismos como por exemplo *Staphylococcus* spp, O objetivo desse trabalho foi realizar uma revisão sistemática sobre a eficácia de anestésicos locais como agente antimicrobiano contra *Staphylococcus* spp. As buscas foram realizadas nas bases de dados Pubmed, Web of science, Scopus, Embase e Lilacs. Como critério de inclusão foram selecionados artigos originais completos, ensaios experimentais in vitro com aplicação dos anestésicos selecionados e bactéria do gênero *Staphylococcus* spp. A presente revisão seguiu ao checklist metodológico para a redação de trabalhos reportando revisões sistemáticas pela declaração Prisma. Foi avaliado o risco de viés de acordo com JBI critical appraisal checklist. Foi realizado análise por um modelo de regressão linear simples moderado por anestésico. Essa revisão sistemática foi registrada pela Open Science Framework- OSF (DOI 10.17605/OSF.IO/C5JM7). Inicialmente foram encontrados 1141 artigos, entretanto, foram analisados 52 artigos após seleção criteriosa. A lidocaína foi o anestésico mais aplicado, sendo avaliado em 35 dos artigos. *S. aureus* ATCC 25923 foi o microrganismo padrão em 17 artigos. Foi avaliado o impacto da concentração do anestésico em relação ao efeito antimicrobiano e os resultados demonstraram que não houve diferença estatisticamente significativa ($F [5, 12] = 0,688$ $p = 0,642$), mesmo quando levado em consideração o efeito moderado pelos anestésicos individualmente. Diante disso, apesar de ter sido demonstrado o efeito antimicrobiano dos anestésicos locais em 82,7% dos estudos avaliados foi encontrado uma grande heterogeneidade dos resultados o que impossibilitou a realização de meta-nálise e futuras recomendações baseadas em evidências.

Palavras-chave: Lidocaína, antimicrobiano, bactericida

1.INTRODUÇÃO

O gênero *Staphylococcus* inclui muitas espécies que fazem parte da microbiota humana. A espécie mais destacada e comum é *Staphylococcus aureus* que contribui para várias infecções além de resultar em alta mortalidade. Acredita-se também que ela esteja envolvida com cerca de 75% das infeções ortopédicas e 18,9% das infecções do sítio cirúrgico [1, 2].

As infecções por *S. aureus* são particularmente problemáticas devido à ocorrência frequente de resistência a antibióticos, entre os quais *Staphylococcus aureus* resistente à meticilina (MRSA) são os mais relevantes clinicamente. As infecções por MRSA são acompanhadas pelo aumento da mortalidade, morbidade e permanência hospitalar, em comparação com aquelas causadas por *Staphylococcus aureus* sensível à meticilina (MSSA) [2-4].

A introdução de antibióticos na prática clínica foi um dos maiores avanços médicos do século 20. Além de tratar doenças infecciosas, os antibióticos possibilitaram muitos procedimentos médicos, incluindo tratamento de câncer, transplantes de órgãos e procedimentos cirúrgicos. No entanto, o uso inadequado desses compostos resultou no rápido aumento da resistência antimicrobiana [5-7].

Mais de 2,8 milhões de infecções resistentes a antibióticos ocorrem nos Estados Unidos a cada ano, e estão associadas a 35.000 mortes. As crescentes taxas de resistência antibacteriana impactam vários aspectos na medicina, além de comprometer o tratamento e prognóstico do paciente. Além disso, também pode resultar em aumento de custos econômicos devido um período prolongado de internação, necessidade de acompanhamento ambulatorial e custos relacionados ao desenvolvimento de novos medicamentos [6, 8, 9].

A identificação de novos tratamentos antimicrobianos é um desafio que exige a colaboração organizações nacionais, internacionais e a indústria farmacêutica. Há 45 novos potenciais antibióticos na fase 3 de ensaios clínicos, sendo estes considerados novas classes com diferentes mecanismos de ação [5]. Vários produtos naturais tem sido relatado por apresentar atividades *in vitro* promissoras contra microrganismos multirresistentes [10]. Entretanto, o desenvolvimento de novos medicamentos pode levar aproximadamente dez anos e gerar custos em torno de um bilhão de dólares. Estratégias alternativas podem servir de atalho nesse processo como o reposicionamento de medicamentos. Neste caso, medicamento aprovados podem ser testados para novas indicações. A grande vantagem é reduzir custos e

acelerar os prazos de aprovação, uma vez que já existem dados de estudos pré-clínicos e de farmacocinética, farmacodinâmica e toxicidade [2, 7, 11].

Os anestésicos locais (AL) são amplamente utilizados na clínica médica para analgesia. Os ALs bloqueiam principalmente os canais de Na+ e K+ dependentes de voltagem, e desta maneira bloqueia a transmissão nervosa e produz anestesia local. A fórmula química dos ALs consiste em anéis aromáticos, grupos amino e cadeias intermediárias. De acordo com as cadeias intermediárias, os ALs são divididos em ésteres como procaína, tetracaína e amidas como lidocaína, ropacaína e bupivacaína. Os ALs podem ser usados sozinhos ou em combinação com anestésicos gerais. A terapia combinada reduz a dose de anestésicos gerais, melhora o efeito anestésico. É notado também que os anestésicos locais podem reduzir a resposta ao estresse neuroendócrino e a imunossupressão perioperatória, além de inibir diretamente a proliferação e metástase de células tumorais [12-14].

Além dos efeitos analgésicos e anestésicos, vários estudos demonstraram que os anestésicos locais apresentam atividade antimicrobiana [15-17]. Esse fato é bastante relevante uma vez que durante a administração anestésica, infecções podem ser advindas tanto da microbiota cutânea do paciente quanto da contaminação pelo profissional de saúde. Como resultado, pode haver infecção de ferida cirúrgica com prejuízo na evolução do paciente. Dessa forma, os anestésicos locais com efeito antimicrobiano podem reduzir esse risco de infecção no paciente [18]. Além disso, podem se tornar uma alternativa atrativa contra patógenos resistentes a antimicrobianos [6,8,9].

Os protocolos com a aplicação dos anestésicos locais com efeito antimicrobiano não são claros quanto as características da população do estudo, intervenções e resultados entre os estudos [15-18]. Esse fato compromete o uso dos anestésicos locais como substâncias antimicrobianas. Além disso, não há relatos de revisão sistemática ou meta-análise que deem embasamento científico sobre sua aplicação.

A revisão sistemática busca sintetizar resultados de estudos sobre benefícios e efeitos adversos baseando-se em estudos disponíveis de boa qualidade. Além disso, provê evidência científica para a tomada de decisão não só de clínicos, mas de planejadores e gerentes [19]. Desta maneira, esse trabalho teve como objetivo avaliar a ação antimicrobiana dos anestésicos locais em relação a *Staphylococcus* spp. por meio de uma revisão sistemática.

2. METODOLOGIA

Essa revisão sistemática foi registrada pela base de dados internacional de revisões sistemáticas em saúde e assistência social Open Science Framework- OSF ((DOI

10.17605/OSF.IO/C5JM7). A presente revisão seguiu ao checklist metodológico para a redação de trabalhos reportando revisões sistemáticas escopo e meta-análises pela declaração PRISMA [20]. O registro prospectivo de protocolos de revisão sistemática aumenta a confiabilidade e transparência na condução do estudo [21].

2.1.Estratégia de pesquisa

Foram consultadas as bases de dados Pubmed, Web of science, Scopus, Embase e Lilacs, por meio dos descritores MeSH (Medical Subject Heading) e operadores boleanos OR e AND. Os termos e palavras chave utilizados para aperfeiçoar a busca foram relacionados chloroprocaine, Prilocaine, bupivacaine, articaine, lidocaine, ropivacaine, local anaesthetics, *Staphylococcus*. Foram incluídos os artigos indexados nas respectivas bases de dados. A coleta foi realizada no período de dezembro de 2020 a outubro de 2021.

2.2.Critérios de elegibilidade e seleção dos estudos

O presente estudo é uma revisão sistemática da literatura sobre evidências da ação antimicrobiana de anestésicos locais, baseando-se nas seguintes etapas: 1) seleção da pergunta temática (elaboração da questão-guia), 2) determinação dos critérios de inclusão e exclusão, 3) triagem dos artigos (seleção da amostra), 4) avaliação dos estudos incluídos, 5) interpretação dos resultados e apresentação da revisão e síntese do conhecimento.

A Questão elaborada foi: Os anestésicos locais possuem ação antimicrobiana frente a *Staphylococcus* spp.? Como critério de inclusão foram selecionados artigos originais completos, ensaios experimentais in vitro com aplicação dos anestésicos selecionados e bactéria do gênero *Staphylococcus* spp.

O desfecho primário foi a redução da população microbiana da espécie *Staphylococcus* spp. com a utilização de anestésicos locais. Como desfecho secundário foi observado os tipos de anestésicos locais e concentração utilizada.

O processo de seleção dos estudos foi realizado por dois revisores independentes (HBB e LFG). Após a exclusão de duplicatas, títulos e resumos foram excluídos de acordo com os critérios de elegibilidade. Após a exclusão por título e resumo, os textos completos dos estudos selecionados foram examinados. Caso necessário, um terceiro revisor (ICP) foi consultado. As listas de referência dos estudos incluídos foram analisadas para obter estudos potencialmente elegíveis que não foram encontrados pela estratégia de busca.

2.3.Extração de dados e análise de dados

A coleta dos dados foi realizada por dois pesquisadores seguindo os critérios de inclusão de forma independente independentes (HBB e LFG) e, posteriormente, os resultados foram confrontados e julgados por um terceiro revisor (ICP) quando necessário. Foram excluídos os artigos que não se enquadravam nos critérios citados.

O processo de extração de dados foi realizado por meio de um formulário padronizado, que incluiu detalhes como nomes dos autores, ano de publicação, local do estudo, microrganismo utilizado, método para avaliar efeito antimicrobiano, resultado principal e financiamento.

Os estudos foram agrupados em três grandes grupos de métodos microbiológicos para avaliar o efeito antimicrobiano: 1) contagem em placa, 2) concentração inibitória mínima (CIM) e 3) métodos variados (Densidade óptica, halo de inibição, contagem bactericida mínima entre outros).

2.4. Avaliação do Risco de viés

Foi realizada uma análise qualitativa dos estudos que preencheram os critérios de inclusão de acordo com a avaliação de risco de viés do Joanna Briggs Institute (JBI), por meio do JBI critical appraisal checklist para estudos quase-experimentais [22].

No JBI critical appraisal checklist, cada pergunta deve ser respondida através de quatro opções: isto é, sim (S), não (N), incerto (I) e não aplicável (NA). O cálculo da porcentagem de risco de viés é feito pela quantidade de “S” que foi selecionada na checklist. Quando a resposta “NA” foi selecionada, a questão não foi considerada no cálculo, de acordo com as diretrizes do Joanna Briggs Institute. Até 49% considera-se um risco alto de viés. De 50% a 70% o risco é moderado e acima de 70% o risco de viés é baixo [23].

2.5. Análise dos dados

Nos estudos que abordaram contagem em placa foi realizada uma subdivisão por tipo de anestésico e avaliado o efeito antimicrobiano por meio do cálculo da porcentagem de redução das unidades formadoras de colônia. Para cada grupo foi calculado a média, desvio padrão e coeficiente de variação. Esses dados também foram utilizados com o objetivo de entender o impacto da concentração do anestésico (%) nas porcentagens de inibição. Como foi incluído no estudo três anestésicos diferentes, Lidocaína, Bupivacaína e Ropicavaína, optou-se pela análise por um modelo de regressão linear simples moderado pelo anestésico

[24]. A análise foi realizada no software *R*, implementado do pacote *MACRO PROCESS V. 4,1*

Nos estudos que adotaram o método CIM para avaliação da ação antimicrobiana foram computados os valores obtidos e em seguida agrupados por anestésico. Para cada grupo foi calculado a média, desvio padrão e coeficiente de variação.

Foi realizada também uma análise dos resultados do método contagem em placa e CIM para a espécie mais predominante (*S. aureus* ATCC 25923) quanto à dispersão dos resultados. No grupo de técnicas variadas foi realizada apenas análise descritiva.

3. RESULTADO

Foram encontrados um total de 1141 artigos. Os artigos foram excluídos em ferramenta de gerenciamento de referências Zotero devido: Duplicação (311) e não adequação por título e resumo (721). Restaram 109 artigos completos. Após a leitura completa restaram 52 artigos (Figura 1).

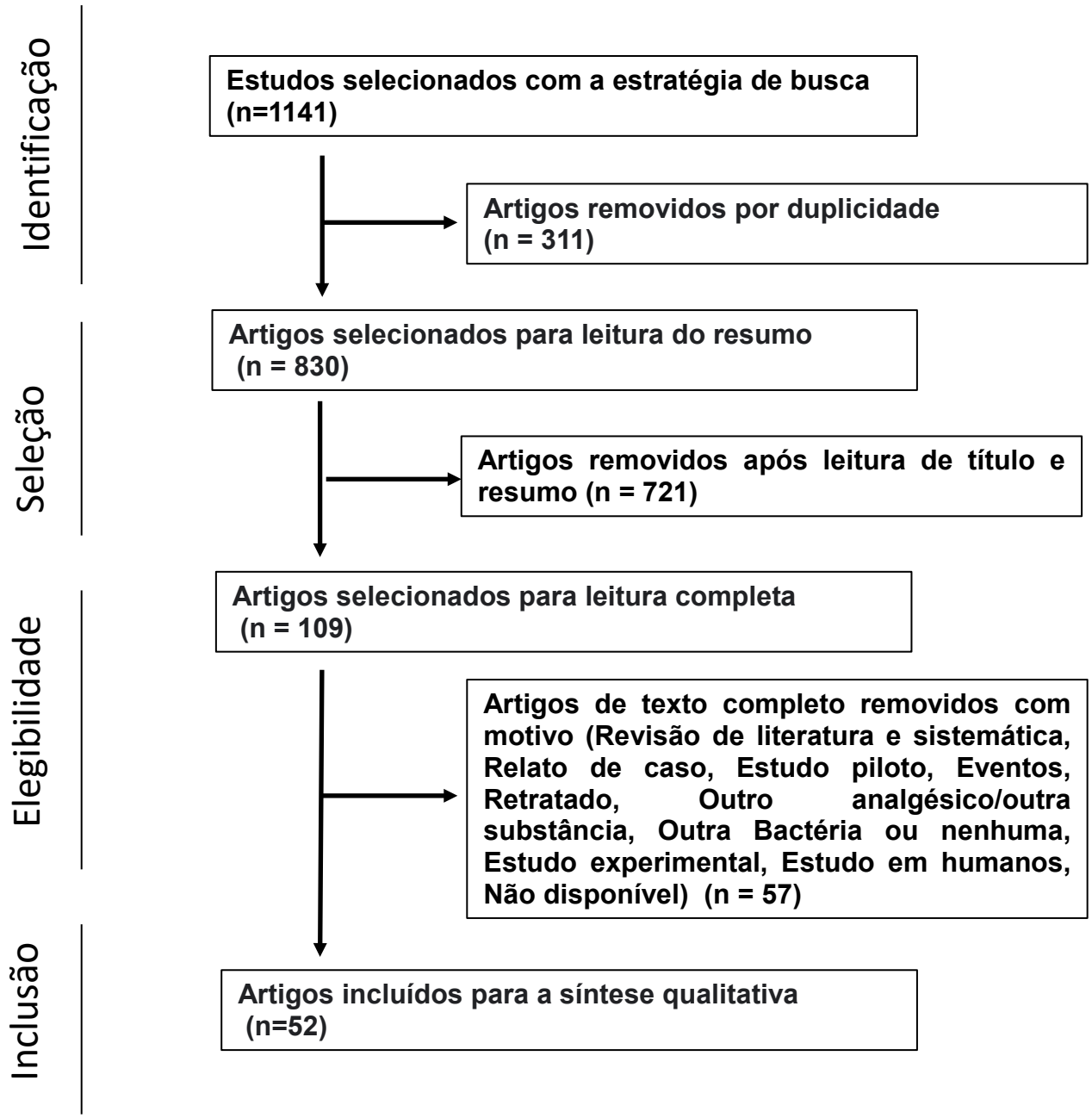

Figura 1. Diagrama de identificação e seleção de artigos adaptado do método Prisma.

Os 52 estudos selecionados foram avaliados e reagrupados de acordo com a metodologia utilizada (Tabela 1). Desta maneira, foi observado 21 artigos que utilizaram a técnica de contagem em placa, 16 artigos para a técnica de CIM e 15 artigos para métodos variados. Os estudos foram realizados em 3 continentes diferentes: Europa (24), América (23) e Ásia (5). A lidocaína foi o anestésico mais aplicado, sendo avaliado em 35 dos artigos. *S. aureus* ATCC 25923 foi o microrganismo padrão em 17 artigos. Apenas 9 artigos não relataram efeito antimicrobiano vinculado ao uso dos anestésicos (4 pela técnica contagem em placa, 1 pelo método CIM e 4 por técnicas variadas). O financiamento dos estudos foi relatado em 15 deles, entretanto, apenas um foi vinculado a indústria de suprimentos médicos.

Tabela 1. Características principais dos estudos

continua

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
1	Adler (2017) [15]	Dinamarca	*S. aureus*	Bupivacaína Lidocaína Mepivacaína	CIM	Concentrações clinicamente aplicadas de bupivacaína, lidocaína e mepivacaína inibiram o crescimento respectivamente de 93%, 93% e 80% dos isolados testados.	Apoiado pelo Danish Government PhD grant The Danish Horse Levy Foundation (Hesteafgiftsfonden)
2	Aldous (1998) [25]	EUA	*S.aureus* ATCC 25923	Lidocaína	CIM	Lidocaína apresentou atividade inibitória contra *S. Aureus.*	Não houve fontes específicas de financiamento para este estudo.
3	Altan (2019) [17]	Peru	*S.aureus* ATCC 25923	Lidocaína	Contagem em placas	A lidocaína inibiu o crescimento de microrganismos.	Não houve fontes específicas de financiamento para este estudo.
4	Aydin (2001) [26]	Peru	*S. aureus*	Lidocaína	Contagem em placas	A lidocaína não afetou o crescimento microbiano.	Não houve fontes específicas de financiamento para este estudo.
5	Aydin (2002) [27]	Peru	*S. aureus* ATCC 25923	Lidocaína Ropivacaína Bupivacaína Prilocaína	Contagem em placas	A ropivacaína não apresentou efeito antimicrobiano. A bupivacaína mostrou baixa eficácia antimicrobiana. Lidocaína e prilocaína tiveram efeitos antimicrobianos mais poderosos do que os outros dois anestésicos locais.	Não houve fontes específicas de financiamento para este estudo.
6	Bátai (2002) [28]	Hungria	*S. aureus* ATCC 23923	Ropivacaína	Contagem em placas	Ropivacaína inibiu completamente o crescimento de *S. aureus.*	Apoiado em partes pelo Ministry of Health of Hungary Grant Number 385/2000/ETT.
7	Bátai (2009) [29]	Hungria	*S. epidermidis*	Lidocaína Prilocaína	Ação antimicrobiana de creme de prilocaína e lidocaína (EMLA)	A microbiota da pele diminuiu significativamente após o tratamento com EMLA.	Apoiado pelo Department of Anesthesiology and Intensive Care and Department of Medical Microbiology.
8	Begec (2007) [30]	Peru	*S. aureus* ATCC 25923	Lidocaína	Densidade óptica (540 nm)	Lidocaína inibiu significativamente a crescimento de *S aureus.*	Não houve fontes específicas de financiamento para este estudo.

Tabela 1. Características principais dos estudos

continação

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
9	Berg (2006) [31]	Dinamarca	*S. aureus* MRSA	Lidocaína	Contagem em placas	As contagens de *S. aureus* foi significativamente reduzidas.	Apoiado por uma bolsa do Regional Institute for Health Sciences, University of Southern Denmark (Su-365-01)
10	Beschastnov (2021) [32]	Rússia	*S. aureus*	Lidocaína	Bacteriófagos	A atividade de *S. aureus* persiste quando os fagos são combinados com ácido succínico e lidocaína.	Não houve fontes específicas de financiamento para este estudo.
11	Boden (2008) [33]	EUA	*S. aureus*	Lidocaína	Contagem em placas	O número de unidades formadoras de colônias (UFCs) foi semelhante no grupocontrole e tratado com lidocaína.	Não houve fontes específicas de financiamento para este estudo.
12	Böttcher (2011) [34]	Alemanha	*S. epidermidis*	Ropivacaína Bupivacaína	Análise de estabilidade microbiológica deanestésicos	Foi mostrado que o reabastecimento repetitivo das seringas não resultou em qualquer contaminação microbiológica, indicando oefeito antimicrobiano dos anestésicos.	Não houve fontes específicas de financiamento para este estudo.
13	Catanzano (2011) [35]	Reino Unido	*S. aureus* ATCC 25913	Lidocaína	Curativos de ácido hialurônico (HA)carregados com lidocaína (LID) e AgNPs	Os dispositivos com LID não apresentaramefeito antimicrobiano.	Não houve fontes específicas de financiamento para este estudo.
14	Coghlan (2009) [36]	Austrália	*S. aureus* ATCC 25923, *S. aureus* ATCC 29212	Bupivacaína Ropivacaína Levobupivacaína	CIM	A bupivacaína apresentou atividadeantibacteriana contra *S. aureus* Ropivacaína e Levobupivacaína não demonstrar atividade contra *S. aureus.*	Não houve fontes específicas de financiamento para este estudo.
15	Cook (1998) [37]	Reino Unido	*Staphylococcus* sp.	Bupivacaína	Contagem em placas	Foi observada ação bactericida.	Não houve fontes específicas de financiamento para este estudo.

Tabela 1. Características principais dos estudos

continuação

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
16	Craig (1999) [38]	EUA	*S. aureus*	Lidocaína	CIM	A concentração inibitória mínima foi superior a 0,5% de lidocaína.	Não houve fontes específicas de financiamento para este estudo.
17	Dory (1985) [39]	Bélgica	*S. aureus*	Lidocaína	Contagem em placas	A lidocaína teve umefeito antibacteriano.	Não houve fontes específicas de financiamento para este estudo.
18	Gajdács (2020) [40]	Hungria	*S. aureus* ATCC 25923	Lidocaína	CIM	Lidocaína demonstrou atividade antibacteriana.	Apoiado por uma bolsa do János Bolyai Research Scholarship of the Hungarian Academy of Sciences (BO/00144/20/5).
19	Gil (2019) [16]	EUA	*S. aureus* ATCC 14775	Lidocaína Bupivacaína	Método "Time Kill"	As combinações de bupivacaína/lidocaína e cetorolaco/gentamicina produziram índicesFIC abaixo de 0,4 – indicativo de efeito antibacteriano sinérgico.	Financiado pelo Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Medical Research Program under Award No. W81XWH-17-1-0614.
20	Gocmen (2008) [41]	Peru	*S. aureus* ATCC 29213	Lidocaína	Halo de inibição	Lidocaína revelou atividade antibacteriana contra *S.aureus.*	Não houve fontes específicas de financiamento para este estudo.
21	Goodman (2002) [42]	EUA	*S. aureus* ATCC 25923	Bupivacaína Ropivacaína Lidocaína	CIM	As concentrações inibitórias mínimas que poderiam inibir o crescimento de S. aureus foram 0,25% de bupivacaína, 1,25% de lidocaína e 0,75% de cloroprocaína.	Não houve fontes específicas de financiamento para este estudo.
22	Grimmond (1986) [43]	Austrália	*S. aureus* ATCC 25923	Bupivacaína	CIM	A concentração inibitória mínima encontrada para bupivacaína foi de 5mg/ml.	Não houve fontes específicas de financiamento para este estudo.
23	Hodson (1999) [44]	Reino Unido	*S. aureus* NCTC 6571	Levobupivacaina Bupivacaína	CBM	A CBM do anestésico local foi 0,25% para bupivacaína e 0,5% para levobupivacaína.	Não houve fontes específicas de financiamento para este estudo.

Tabela 1. Características principais dos estudos

continuação

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
24	Imani (2020) [45]	Irã	*S. epidermidis* ATCC12228	Bupivacaína Lidocaína	Contagem em placas	Lidocaína e bupivacaína apresentaram um forte efeito inibitório no crescimento de *S. epidermidis* ATCC12228	Apoiado pela Iran University of Medical Sciences, Iran
25	James (1976) [46]	Inglaterra	*S epidermidis*	Bupivacaína	Contagem em placas	Bupivacaína apresentou efeito bactericida	Não houve fontes específicas de financiamento para este estudo.
26	Kampe (2003) [47]	Alemanha	*S. aureus* ATCC 25923	Ropivacaína	Contagem em placas	O crescimento de *S.aureus* foi significativamente menor na presença de ropivacaína	Não houve fontes específicas de financiamento para este estudo.
27	Kesici (2019a) [48]	Peru	*S. aureus* ATCC 29213	Prilocaína Bupivacaína	CIM	Ambos os anestésicos apresentaram efeito antibacteriano. Verificou-se que a prilocaína teve um maior potencial de efeito antibacteriano sobre *S. aureus* em comparação com a bupivacaína.	Não houve fontes específicas de financiamento para este estudo.
28	Kesici (2019b) [18]	Peru	*S. aureus* ATCC 29213	Lidocaína	CIM	O valor de concentração inibitória mínima para lidocaína foi 20 mg/mL.	Não houve fontes específicas de financiamento para este estudo.
29	Kesici (2019c) [49]	Peru	*S.aureus* ATCC 29213	Lidocaína	CIM	O valor de concentração inibitória mínima para lidocaína foi 20 mg/mL.	Não houve fontes específicas de financiamento para este estudo.
30	Kesici (2020) [50]	Turquia	*S. aureus* ATCC 29213	Bupivacaína	CIM	Os valores de CIM foram superiores a 20 mg/mL.	Não houve fontes específicas de financiamento para este estudo.
31	Kiefer (2003) [51]	Alemanha	*S. aureus* ATCC 25923	Lidocaína, Bupivacaína Ropivacaína	Ensaios laboratoriais para avaliar parametros de defesa antibacteriana no hospedeiro	A capacidade dos granulócitos de ingerir bactérias foi significativamente deprimida apenas pela lidocaína ($p<0,003$).	Não houve fontes específicas de financiamento para este estudo.

Tabela 1. Características principais dos estudos

continuação

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
32	Kleinbeck (2009) [52]	EUA	*S. aureus* 6538P	Bupivocaína	Método fotopolimerizadas in situ (sIPNs)	Os sIPNs liberam efetivamente bupivacaína e sulfadiazina de prata, mantendo a atividade antimicrobiana da sulfadiazina de prata.	Apoiado por subvenções do NIH O1EB6613 and UW-Madison I&EDR.
33	Kleinfeld (1966) [53]	EUA	*S. aureus*	Tetracaína	Contagem em placas	Tetracaína, 0,3%, inibiu efetivamente *S. aureus*.	Apoiado em partes pelo US Public Health Service grant 2 Tl NB 5367-06 from the National Institutes of Health.
34	Labetoulle (2002) [54]	França	*S. aureus* CIP103911	Lidocaína	CIM	Lidocaína a 1% permitiu o crescimento bacteriano.	Não houve fontes específicas de financiamento para este estudo.
35	López-Iglesias (2020) [55]	Portugal	*S. aureus* ATCC 33591	Lidocaína	Carreamento de lidocaína em micropartículas lipídicas sólidas (SLMPs)	SLMPs apresentaram atividade antimicrobiana em *S. aureus.*	Financiado pela Xunta de Galicia [ED431F 2016/010], MCIUN [RTI2018-094131-A-I00], Agrupación Estratégica de Materiales [AeMAT-BIOMEDCO2, ED431E 2018/08], Agencia Estatal de Investigación [AEI] e FEDER funds. MINECO for a Ramón y Cajal Fellowship [RYC2014-15239]. Parcialmente apoiado pelo Programa de Actividades de I+D entre Grupos de Investigación de la Comunidad de Madrid [S2018/BAA-4480, Biopieltec-CM], Programa Estatal de I+D+I Orientada a los Retos de la Sociedad [RTI2018-101627-B-I00] and Cátedra Fundación Ramón Areces.

Tabela 1. Características principais dos estudos

continuação

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
36	Nai (2021) [56]	Brasil	*S. aureus* ATCC 25923	Lidocaína	Dimensão fractal	Lidocaína inibiu o crescimento de *S. aureus* em próteses.	Financiado por fundos de pesquisa da Universidade do Oeste Paulista (UNOESTE).
37	Neuwersch (2017) [57]	Áustria	*S. aureus*	Lidocaína Mepivacaína Bupivacaína Ropivacaína	Halo de inibição	O anestésico local não demonstrou zona de inibição.	Não houve fontes específicas de financiamento para este estudo.
38	Parr (1999) [58]	Canadá	*S. aureus* ATCC 29213	Lidocaína	CIM	A CIM para lidocaína foi 4g/100mL.	Não houve fontes específicas de financiamento para este estudo.
39	Pelz (2008) [59]	Alemanha	*S. aureus* ATCC 25923	Bupivacaína Mepivacaína Prilocaína Lidocaína	CIM	Os valores de CIM de todos os anestésicos locais ficaram entre 0,25 e 16 mg/mL.	Não houve fontes específicas de financiamento para este estudo.
40	Reynolds (2016) [60]	EUA	*S. epidermidis*	LidocaínaTetracaína Proparacaína	CIM	A lidocaína apresentou CIM de 4,27 a 8,53 $x10^5$ mol/mL. A tetracaína apresentou CIM de 9,45 x 10^6 mol/mL.	Apoiado em parte por doações irrestritas da Research to Prevent Blindness, Inc. the Deshong Family, and Vitreoretinal Surgery Foundation Minneapolis, MN.
41	Rosenberg (1985) [61]	Finlândia	*S. aureus* ATCC 23923	Bupivacaína	Contagem em placas	A bupivacaína inibe o crescimento de *S. aureus*.	Não houve fontes específicas de financiamento para este estudo.
42	Sakuragi (1997) [62]	Japão	*S. aureus* ATCC 25923	Bupivacaína	Contagem em placas	*S. aureus* reduziu a contagem de colônias em 96,0% quando exposto à bupivovocaína.	Não houve fontes específicas de financiamento para este estudo.
43	Sakuragi (1998) [63]	Japão	*S. aureus* ATCC 25923	Bupivacaína	Contagem em placas	*S. aureus* reduziu a contagem média de colônias em até 99,9% quando exposto à bupivacaína.	Não houve fontes específicas de financiamento para este estudo.

Tabela 1. Características principais dos estudos

conclusão

Nº	Primeiro autor/ ano	Local	Microrganismo	Anestésico	Método	Resultados	Financiamento
44	Schweitzer (1995) [64]	EUA	*S. aureus*	Lidocaína	CIM	As concentrações inibitórias mínimas de lidocaína foram >5,0mg/ml para *S. aureus.*	Não houve fontes específicas de financiamento para este estudo.
45	Sculley (1980) [65]	Irlanda	*S. aureus*	Lidocaína	Contagem em placas	Um efeito bactericida foi observado contra *S. aureus.*	Não houve fontes específicas de financiamento para este estudo.
46	Srisatjaluk (2016) [66]	Tailândia	*S. aureus* ATCC 6538	Lidocaína	Spray e halo de inibição	Lidocaína não apresentou efeito bactericida contra *S. aureus.*	Parcialmente apoiada pela Faculty of Dentistry, Mahidol University.
47	Tamanai-Shacoori (2004) [67]	França	*S. aureus* ATCC 9144	Bupivacaína Ropivacaína	Contagem em placas	A bupivacaína inibiu o crescimento de *S. aureus* (22 ± 3,6%). Ropivacaína também inibiu o crescimento de *S. aureus* (25,5 ± 4,1%).	Não houve fontes específicas de financiamento para este estudo.
48	Tolentino (2009) [68]	Brasil	*S. aureus*	Lidocaína	Contagem em placas	Foi observado que lidocaína possui forte efeito antimicrobiano.	Não houve fontes específicas de financiamento para este estudo.
49	Vidovich (1999) [69]	EUA	*S. aureus* ATCC 29213	Lidocaína	Contagem em placas	A lidocaína apresentou propriedades antibacterianas.	Não houve fontes específicas de financiamento para este estudo.
50	Wachowski (1999) [70]	Canadá	*S. aureus* ATCC 25923	Lidocaína	Contagem em placas	O efeito da lidocaína não diferiu dos efeitos da solução isotônica de cloreto de sódio isoladamente (Controle).	Apoiado em partes por uma subvenção da Edmonton Northern Anesthetists' Society.
51	Williams (1997) [71]	EUA	*S. aureus*	Lidocaína	Contagem em placas	As contagens de *S. aureus* demonstraram pouca entre os controles e diferentes concentrações de lidocaína	Apoiado em parte por uma subvenção irrestrita da Wells-Johnson Company, Tucson, Ariz.
52	Zaidi (1977) [72]	Reino Unido	*S. aureus* NCTC 6571	AmetocaínaBupivacaína Cocaína Lignocaína Prilocaína Procaína	CBM	Todos os anestésicos inibiram o crescimentoacteriano quando testados sem diluição.	Não houve fontes específicas de financiamento para este estudo.

Todos os artigos foram analisados com a *JBI critical appraisal checklist* para estudos quase-experimentais (tabela 2). Foi observado que 43 artigos apresentaram baixo risco de viés e apenas um artigo mostrou alto risco de viés, que por um acaso não observou o efeito antimicrobiano da lidocaína.

Dentre as principais limitações dos estudos foi observado a ausência de várias medições do resultado antes e depois da intervenção/exposição (Q5-55,7%) e análise estatística inapropriada (Q9 – 46,1%) que impactaram na qualidade dos estudos e da realização da meta-análise. Todos os trabalhos apresentaram causa/efeito além das amostras serem comparadas, tratadas e medidas de maneira semelhantes (Q1, Q2, Q3 e Q7).

Tabela 2. – Resultados da avaliação do risco de viés dos estudos incluídos usando a ferramenta do Joanna Briggs Institute (JBI) para estudos quase-experimentais

continua

	Estudos	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Porcentagem Risco de Vies
1	Adler (2017) [15]	S	S	S	N	NA	N	S	S	N	55,56
2	Aldous (1998) [25]	S	S	S	S	NA	S	S	S	N	77,78
3	Altan (2019) [17]	S	S	S	S	S	S	S	S	S	100,00
4	Aydin (2001) [26]	S	S	S	S	S	S	S	S	S	100,00
5	Aydin (2002) [27]	S	S	S	S	NC	NC	S	S	S	77,78
6	Bátai (2002) [28]	S	S	S	S	S	S	S	S	S	100,00
7	Bátai (2009) [29]	S	S	S	S	S	S	S	S	S	100,00
8	Begec (2007) [20]	S	S	S	S	S	S	S	S	S	100,00
9	Berg (2006) [31]	S	S	S	S	S	S	S	S	S	100,00
10	Beschastnov (2021) [32]	S	S	S	S	NA	S	S	S	N	77,78
11	Boden (2008) [33]	S	S	S	N	N	N	S	N	N	44,44
12	Böttcher (2011) [34]	S	S	S	S	NA	N	S	S	N	66,67
13	Catanzano (2011) [35]	S	S	S	S	S	S	S	S	S	100,00
14	Coghlan (2009) [36]	S	S	S	N	NA	S	S	S	N	66,67
15	Cook (1998) [37]	S	S	S	S	S	S	S	N	N	77,78
16	Craig (1999) [38]	S	S	S	S	NA	S	S	S	S	88,89
17	Dory (1985) [39]	S	S	S	S	S	NC	S	N	N	66,67
18	Gajdács (2020) [40]	S	S	S	S	NA	S	S	S	N	77,78
19	Gil (2019) [16]	S	S	S	S	S	N	S	S	N	77,78
20	Gocmen (2008) [41]	S	S	S	N	NA	S	S	S	S	77,78
21	Goodman (2002) [42]	S	S	S	S	NA	S	S	S	N	77,78
22	Grimmond (1986) [43]	S	S	S	N	NA	S	S	S	N	66,67
23	Hodson (1999) [44]	S	S	S	S	S	S	S	S	S	100,00
24	Imani (2020) [45]	S	S	S	N	N	S	S	S	S	77,78
25	James (1976) [46]	S	S	S	S	S	S	S	N	N	77,78
26	Kampe (2003) [47]	S	S	S	S	S	S	S	S	S	100,00

Tabela 2. – Resultados da avaliação do risco de viés dos estudos incluídos usando a ferramenta do Joanna Briggs Institute (JBI) para estudos quase-experimentais

conclusão

	Estudos	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Porcentagem Risco de Vies
27	Kesici (2019a) [48]	S	S	S	S	NA	S	S	S	S	88,89
28	Kesici (2019b) [18]	S	S	S	S	NA	S	S	S	S	88,89
29	Kesici (2019c) [49]	S	S	S	S	NA	S	S	S	S	88,89
30	Kesici (2020) [50]	S	S	S	S	NA	S	S	S	S	88,89
31	Kiefer (2003) [51]	S	S	S	S	S	S	S	S	S	100,00
32	Kleinbeck (2009) [52]	S	S	S	N	S	S	S	S	S	88,89
33	Kleinfeld (1966) [53]	S	S	S	S	S	N	S	S	N	77,78
34	Labetoulle (2002) [54]	S	S	S	S	NA	S	S	S	S	88,89
35	López-Iglesias (2020) [55]	S	S	S	S	NA	S	S	S	S	88,89
36	Nai (2021) [56]	S	S	S	S	NA	S	S	S	S	88,89
37	Neuwersch (2017) [57]	S	S	S	N	NA	S	S	S	N	66,67
38	Parr (1999) [58]	S	S	S	S	NA	S	S	S	N	77,78
39	Pelz (2008) [59]	S	S	S	S	NA	S	S	S	N	77,78
40	Reynolds (2016) [60]	S	S	S	S	NA	S	S	S	N	77,78
41	Rosenberg (1985) [61]	S	S	S	N	N	S	S	N	N	55,56
42	Sakuragi (1997) [62]	S	S	S	N	N	S	S	S	S	77,78
43	Sakuragi (1998) [63]	S	S	S	S	N	S	S	S	S	88,89
44	Schweitzer (1995) [64]	S	S	S	S	S	N	S	S	N	77,78
45	Sculley (1980) [65]	S	S	S	S	N	S	S	N	N	66,67
46	Srisatjaluk (2016) [66]	S	S	S	S	S	S	S	S	S	100,00
47	Tamanai-Shacoori (2004) [67]	S	S	S	S	N	S	S	S	S	88,89
48	Tolentino (2009) [68]	S	S	S	S	S	S	S	N	N	77,78
49	Vidovich (1999) [69]	S	S	S	S	S	S	S	S	S	100,00
50	Wachowski (1999) [70]	S	S	S	S	S	S	S	S	S	100,00
51	Williams (1997) [71]	S	S	S	S	S	S	S	N	N	77,78
52	Zaidi (1977) [72]	S	S	S	S	S	N	S	S	N	77,78

Questões do instrumento do JBI, o Critical Appraisal Checklist para estudos quase-experimentais: Q1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)? Q2. Were the participants included in any comparisons similar? Q3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4. Was there a control group? Q5. Were there multiple measurements of the outcome both pre and post the intervention/exposure? Q6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Q7. Were the outcomes of participants included in any comparisons measured in the same way? Q8. Were outcomes measured in a reliable way? Q9. Was appropriate statistical analysis used?

Legenda: S= Sim; N= não; NC= Não Claro; NA= Não Aplicável.

Foram obtidos 21 estudos que utilizaram a técnica de contagem em placa para avaliar o efeito antimicrobiano dos anestésicos (tabela 3). A lidocaína foi avaliada em 11 trabalhos, e

destes, 6 demonstraram que este anestésico reduziu mais de 80% das unidades formadoras de colônia. Entretanto, as concentrações aplicadas variaram de 0,5-5%. O valor médio encontrado para a % de inibição com esse anestésico foi 71,24±34,95% (CV= 49,06).

Tabela 3. Resultados obtidos pela técnica de contagem em placa

Anestésico	Primeiro autor	Ano	Microrganismo	Concentração do anestésico %	% de inibição
Lidocaína	Dory [39]	1985	*S. aureus* (isol. clínicos)	1	100
	Sculley [65]	1980	*S. aureus*	2	0
	Tolentino [68]	2009	*S. aureus*	5	100
	Vidovich [69]	1999	*S. aureus* ATCC 29213	1	31,40
	Altan [17]	2019	*S. aureus* ATCC 25923	1,5	94,40
	Aydin [26]	2001	*S. aureus* ATCC 25923	5	99,80
	Aydin [27]	2002	*S. aureus* ATCC 25923	2	82
	Berg [31]	2006	*S. aureus* ATCC 25923	1	96,60
	Boden [33]	2008	*S. aureus*	-	0
	Wachowski [70]	1999	*S. aureus* ATCC 25923	0,5	63,60
	Williams [71]	1997	*S. aureus*	0,5	14,20
Bupivacaína	Gajdács [40]	2020	*S. aureus* ATCC 25923	0,5	90
	James [46]	1976	*S. epidermidis*	0,25	10
	Rosenberg [61]	1985	*S. aureus* ATCC 25923	0,5	100
	Sakuragi [62]	1997	*S. aureus* ATCC 25923	0,5	100
	Sakuragi [63]	1998	*S. aureus* ATCC 25923	0,5	100
	Aydin [26]	2001	*S. aureus* ATCC 25923	0,5	0
	Cook [37]	1998	*Staphylococcus* sp.	0,5	99
Ropivacaína	Kampe [47]	2003	*S. aureus* ATCC 25923	0,1	0
	Aydin [26]	2001	*S. aureus* ATCC 25923	2	0
	Bátai [28]	2002	*S. aureus* ATCC 25923	1	100

Para a análise com uso de bupivacaína foram obtidos sete artigos. Um total de cinco artigos obtiveram redução das unidades formadoras de colônia maior que 90%. Apenas um trabalho utilizou a concentração 0,25%. Foi avaliada o coeficiente de variação da porcentagem de inibição daqueles trabalhos que utilizaram a concentração de bupivacaína de 0,5% e foi obtida média de 78±43,81% (CV=56,17).

A ropivacaína foi avaliada em três estudos, que apesar de terem utilizado o mesmo microrganismo, aplicou três concentrações diferentes de estudo. Nos resultados encontrados, apenas 1 estudo demonstrou efeito antimicrobiano deste anestésico.

A fim de compreender a relação da concentração do anestésico na inibição foi utilizado um modelo com moderador, esse tem o objetivo de avaliar o impacto de uma

variável concentração em inibição em relação a cada moderador (tipo de anestésico) (figura 2).

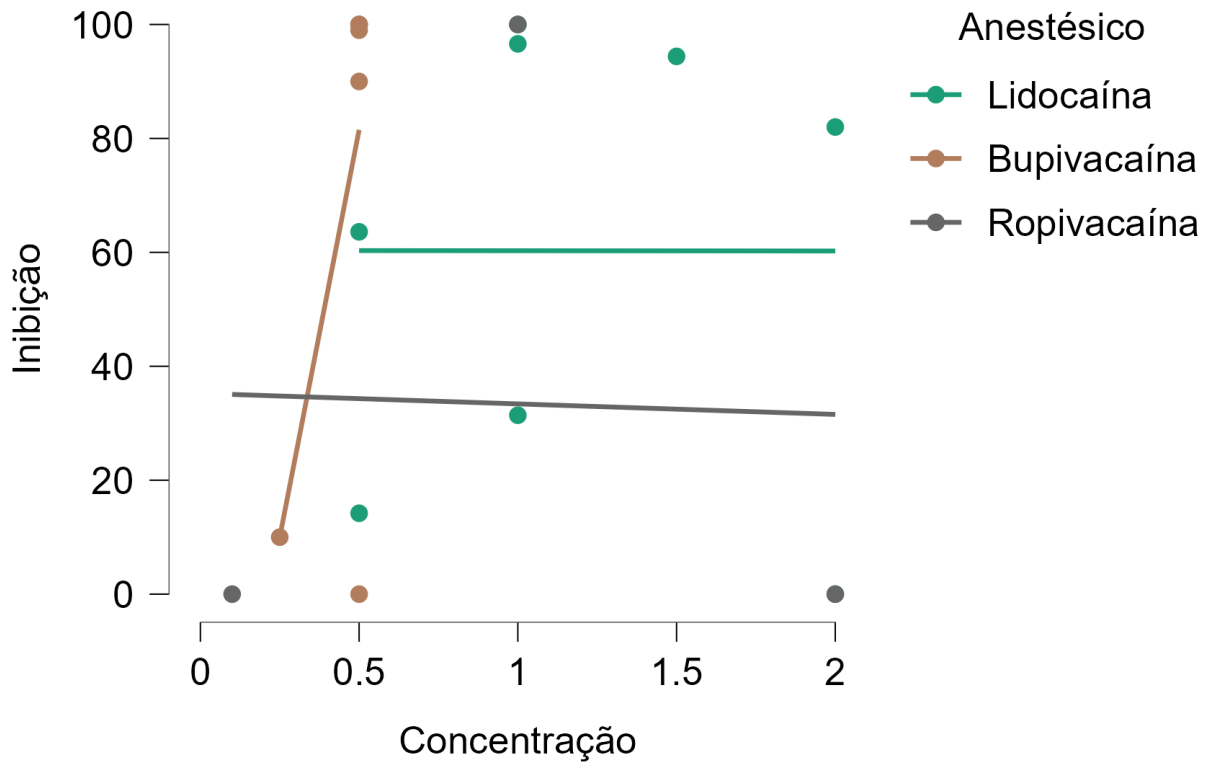

Figura 2 - Regressão linear simples com anestésico como moderador

Apesar da figura 2 sugerir um possível efeito inibitório da Bupivacaína, o modelo não é estatisticamente significativo (F [5, 12] = 0,688 p = 0,642), mesmo quando levado em consideração do efeito moderado pelos anestésicos individualmente (Tabela 4).

Tabela 4 - Coeficientes do modelo moderado

	B	Erro padrão	*B* Padronizado	*T*	*P*
Intercepto	60,329	38,721		1,558	0,145
Concentração	-0,046	29,535	-6,305e-4	-0,002	0,999
Anestésico (Bupivacaína)	121,829	102,335		-1,190	0,257
Anestésico (Ropivacaína)	-25,089	59,076		-0,425	0,679
Concentração ✻ Anestésico (Bupivacaína)	286,046	202,663		1,411	0,184
Concentração ✻ Anestésico (Ropivacaína)	-1,799	45,435		-0,040	0,969

Os resultados dos 16 artigos que adotaram a técnica de CIM foram agrupados de acordo com o anestésico avaliado (tabela 5). Alguns destes trabalhos avaliaram mais de um anestésico. Foram obtidos 12 trabalhos que avaliaram o efeito antimicrobiano da lidocaína. Os

valores variaram de 0,039 a 40mg/ml com uma média de CIM de 13 ±14,4 mg/ml (CV= 111,11). Seis trabalhos aplicaram a bupivacaína, sendo que estes apresentaram valor de CIM na faixa de 2-20mg/ml com valor médio de CIM de 8,8 ± 8,7 mg/ml (CV= 98,6). Tetracaína foi estudada em 2 artigos e valor médio encontrado foi 0,514 ± 0,68 mg/ml (CV= 133,7). A mepicavaína também foi investigada em 2 artigos e resultou em uma média de 11,54± 4,8 mg/ml (CV= 42,4). A procaína foi estudada em apenas um artigo e resultou em CIM de 0,005mg/ml.

Tabela 5. Resultados obtidos pela técnica de Concentração mínima inibitória

Anestésico	**Primeiro autor/ano**	**Ano**	**Microrganismo**	**Concentração inibitória (mg/ml)**
Lidocaína	Pelz [59]	2008	*S. aureus* ATCC 25923	7
	Reynolds [60]	2016	*S. epidermidis* (isolados clínicos)	0,27
	Adler [15]	2017	*S. aureus* (isolados clínicos)	10
	Aldous [25]	1998	*S. aureus* ATCC 25923	40
	Craig [38]	1999	*S. aureus* (isolados clínicos)	5
	Gajdács [40]	2020	S. *aureus* ATCC 25923	0,250
	Goodman [42]	2002	*S. aureus* ATCC 29213	12,5
	Kesici [18]	2019b	*S. aureus* ATCC 29213	20
	Kesici [48]	2019c	*S. aureus* ATCC 29213	20
	Labetoulle [54]	2002	*S. aureus* CIP658	1
	Parr [58]	1999	*S. aureus* MRSA	40
	López [55]	2000	*S. aureus* ATCC 33591	0,039
Bupivacaína	Adler [15]	2017	*S. aureus* (isolados clínicos)	2,5
	Coghlan [36]	2009	*S. aureus* ATCC 25923	2
	Goodman [42]	2002	*S. aureus* ATCC 29213	3,5
	Grimmond [43]	1986	*S. aureus* ATCC 25923	5
	Kesici [48]	2019a	*S. aureus* ATCC 29213	20
	Kesici [50]	2020	*S. aureus* ATCC 29213	20
Procaína	Reynolds [60]	2016	*S. epidermidis* (isolados clínicos)	0,005
Tetracaína	Reynolds [60]	2016	*S. epidermidis* (isolados clínicos)	0,028
	Labetoulle [54]	2002	*S. aureus* CIP658	1
Mepivacaína	Pelz [59]	2008	*S. aureus* ATCC 25923	8,08
	Adler [15]	2017	*S. aureus* isolates	15

Conforme demonstrado pelos valores de coeficiente de variação, foi observada uma alta heterogeneidade nos resultados obtidos tanto pela contagem em placa quanto pela concentração inibitória mínima. Desta maneira, foi selecionado estudos que avaliaram o efeito dos anestésicos com a espécie *S. aureus* ATCC 25923 para reduzir o número de interferências. Na tabela 6 está demonstrado o valor do coeficiente de variação dos resultados

encontrados, e conforme observado, apenas a na aplicação da lidocaína com o método de contagem em placa foi possível obter um coeficiente de variação moderado. A utilização da ropivacaína também foi avaliada em dois trabalhos. Ambos obtiveram o mesmo resultado (nenhum efeito antimicrobiano - 0% de inibição) portanto, não houve variação entre os resultados. Nas outras condições avaliadas foi obtida uma alta heterogeneidade novamente.

Tabela 6. Dispersão dos resultados do efeito antimicrobiano dos anestésicos pelo método de contagem em placa e CIM em relação a *S. aureus* ATCC 25923

	Contagem em Placa			CIM	
	Lidocaína	Bupivacaína	Ropivacaína	Lidocaína	Bupivacaína
N° artigos	5	5	1	3	2
Média*	87,22	78	0	3,75	3,5
Desvio Padrão	14,97	43,81	0	3,38	2,12
Coeficiente de Variação	17,17	56,17	-	90,18	60,60

*Para a técnica de contagem em placa foi considerada a média da % de inibição de unidades formadoras de colônia e para o método CIM foi considerado a média do valor de CIM

Foram levantados 15 artigos que trabalharam com técnicas variadas para avaliar o efeito antimicrobiano de anestésicos como halo de inibição, densidade óptica, nanopartículas, CBM entre outros. Destes, quatro artigos indicaram que os anestésicos não apresentaram atividade antimicrobiana. O anestésico mais utilizado foi a lidocaína (9).

4. DISCUSSÃO

A ausência de novos tratamentos para infecções desperta grande preocupação de órgãos regulamentadores de Saúde Pública para o desenvolvimento e aplicação de novos agentes antimicrobianos. Vários estudos indicam que anestésicos possuem potencial efeito antimicrobiano e diminuiu significativamente o crescimento de *Staphylococcus* spp. [15, 16, 17]. Fato esse comprovado no presente estudo, uma vez que 82,7% dos artigos obtidos na estratégia de busca demonstraram que anestésicos locais possuem tal efeito, e apenas um artigo foi financiado por empresa relacionada com suprimentos médicos, sugerindo uma alta confiabilidade dos estudos uma vez que não haviam conflito de interesse.

A lidocaína foi o agente anestésico mais estudado (67,3%). Acredita-se que o mecanismo de ação da atividade antimicrobiana dos ALs esteja vinculados a ruptura da membrana celular bacteriana, inibição da síntese da parede celular, disfunção da respiração celular, alteração na síntese de DNA, lise de protoplastos, alteração na permeabilidade e

vazamento de componentes intracelulares, alterações ultraestruturais e inibição de enzimas ligadas à membrana atividades [73].

Apesar do montante de estudos que avaliaram o efeito antimicrobiano dos anestésicos foi observado uma grande heterogeneidade em relação a várias características dos protocolos utilizados como tempo de exposição, diferente concentração, temperatura, estrutura e a característica do microrganismo estudado. Embora os artigos tenham abordado a utilização de vários tipos de anestésicos, não foi evidenciado a concentração e o anestésico mais eficaz para redução do crescimento de *Staphylococcus* spp. conforme observados pela análise de regressão linear. Entretanto, alguns trabalhos de forma independente, ao testar várias concentrações em mesmas condições laboratoriais reforçam uma atividade antimicrobiana contra bactérias Gram-positivas e Gram-negativas dependente da concentração dos anestésicos [16, 17, 73].

Vale ressaltar também que apesar do baixo risco de viés observado nos estudos (82,6%), foi observado limitações, como análise estatística inadequada em cerca de 46% dos artigos, que impactam substancialmente a realização de análises de evidência científica e não permitiu chegar a um consenso sobre a forma correta da utilização dos anestésicos como agente antimicrobiano [74].

No presente estudo foi observado a aplicação de técnicas distintas para avaliar o efeito antimicrobiano, como o método de contagem em placa, CIM, CBM, método fotopolimerizadas *in situ*, time kill e dimensão fractal. A evolução de técnicas laboratoriais proporcionou a adoção de métodos modernos que cada vez mais estão sendo utilizados na área microbiológica. Apesar deste avanço trazer inúmeras vantagens e despertar interesse em pesquisadores, o mesmo pode ser mais dispendioso por exemplo, devido a necessidade de padronização [75, 76].

O método de contagem de placas permite quantificar número de bactérias viáveis em amostras. Embora seja uma técnica que possua vantagens microbiológicas como menor custo, curto tempo de incubação, facilidade de desenvolvimento, ainda apresenta limitações. A possibilidade de erros e a demora da contagem manual em placas diminuiu a precisão dos resultados, além disso, pode não ser contabilizado bactérias viáveis mais não cultiváveis, a diluição seriada pode estar incorreta, as colônias podem apresentar crescimento com tamanhos e cores diferentes, dificultando a sua contagem [75, 77].

CIM é definida como a menor concentração de um agente antimicrobiano em limitar o crescimento visível de um microrganismo. O método é considerado “padrão ouro” para determinar a sensibilidade de inibição do patógeno, sendo amplamente usado como teste de

resistência microbiana [78]. As técnicas que estabelecem CIM e suas execuções são regulamentadas pela Clinical and Laboratory Standards Institute (CLSI) [76, 79]. Entretanto, os artigos apresentaram protocolos sem padrão em relação a temperaturas, meio de cultivo, espécie microbiana, impossibilitando uma definição sobre a concentração inibitória. Desta forma, a diversidade dos resultados apresentados sugere um impasse sobre a compreensão da melhor técnica a ser utilizada na avaliação do efeito antimicrobiano dos anestésicos locais.

Em conclusão, os anestésicos locais tem o potencial de serem aplicados como adjuvantes ao uso antimicrobiano tradicional no ambiente clínico ou laboratorial e na profilaxia de infecção de sítio cirúrgico trazendo vantagens como redução de custos, diminuição do risco de resistência a antimicrobianos e possibilitando novas alternativas para o tratamento de infecções. Entretanto, deve ser considerada a heterogeneidade interindividual na resposta ao tratamento e a possibilidade de resultados falso negativos no cultivo bacteriano quando adotados protocolos inadequados. Ficou evidenciado que a variabilidade dos desenhos experimentais e riscos de viés dos estudos levantados nessa revisão sistemática impossibilitou a realização da meta-análise. Diante disso, novos estudos baseados em protocolos padronizados devem ser direcionados uma vez que são essenciais para futuras recomendações baseadas em evidências científicas.

5. CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

6.CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesses relacionados com o presente trabalho.

7.FONTES DE FINANCIAMENTO

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ANEXO A - PRISMA 2020 CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			07
Title	1	Identify the report as a systematic review.	07
ABSTRACT			08
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	08
INTRODUCTION			09
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	09
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	10
METHODS			10
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	11
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	12
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	12
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	12
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	13
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12,13

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	12,14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	12
RESULTS			13
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	14
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	15
Study characteristics	17	Cite each included study and present its characteristics.	16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	23
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	25,26,27,28
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	23,24
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	27,28
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	27, 28
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	26
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	23,24
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	25,27,28
DISCUSSION			28
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	28
	23b	Discuss any limitations of the evidence included in the review.	28
	23c	Discuss any limitations of the review processes used.	29
	23d	Discuss implications of the results for practice, policy, and future research.	30
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	10
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	10
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	10
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	30
Competing interests	26	Declare any competing interests of review authors.	30
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the	30

Section and Topic	Item #	Checklist item	Location where item is reported
other materials		review.	

ANEXO B - NORMAS DE SUBMISSÃO ADVANCES IN THERAPY

ADIS RAPID+ Instructions for authors

Contents

JOURNAL INFORMATION

For more information on individual Adis Rapid+ journals including aims and scope, publication fees, contact information, and Editorial and Advisory board members, please visit the journal websites.

Advances in Therapy
Cardiology and Therapy
Dermatology and Therapy
Diabetes Therapy
Infectious Diseases and Therapy
Neurology and Therapy
Oncology and Therapy
Ophthalmology and Therapy
Pain and Therapy
Pulmonary Therapy
Rheumatology and Therapy

Please note that there is a Rapid Service Fee associated with publication across the entire Adis Rapid+ journals portfolio. This is a **mandatory** fee that must be paid upon article acceptance. For more information on compulsory fees, please see each journal website, using the links above. Information regarding fees can then be found under the *"Aims and Scopes"* heading on each of the journal websites.

PRESUBMISSION CHECKLIST

Manuscripts should be submitted through the Editorial Manager online submission system. Please ensure that your submission meets our editorial policies by following the below instructions. Prior to submission, please use the below checklists to make sure you have the necessary information and files that are required to submit your manuscript. We cannot proceed with the submission until we receive all of the necessary requirements outlined below.

Further information on how to submit your article can be found here.

Information Checklist

The below details should be given in the appropriate fields in the online submission system:

- ✔ Article type (see here);
- ✔ Article title;
- ✔ Author information, including affiliations, and email addresses for all authors;
- ✔ Abstract (including the trial registration number, if applicable);
- ✔ Three to ten keywords;
- ✔ Confirmation that your submission complies with the following requirements:
  - The manuscript is not being considered for publication by another journal, nor will it be submitted elsewhere while under consideration by this journal;
  - The manuscript has not been published previously (partly or in full);

- No tables/figures/images/other material that infringe the copyright of another publisher/individual are included in the manuscript (or if there are such items included in the manuscript, permission to reproduce [both in print and online for the lifetime of product] has been sought and received for publication in this manuscript);
- All co-authors are aware of the submission to this journal, and agree to allow the corresponding author to serve as the primary correspondent with the editorial office and to review and sign off on the final proofs for publication;
- The authors whose names appear on the submission have contributed sufficiently to the manuscript (concept and planning of the work described; acquisition, analysis and interpretation of the data; drafting and/or critical revision of the manuscript; and approved the final submitted version of the manuscript) and, therefore, share collective responsibility and accountability for the manuscript;
- No deserving authors have been omitted from the authorship list;
- All persons who made substantial contributions to the manuscript but who do not fulfil the authorship criteria are listed with their specific contributions in the Acknowledgements section of the manuscript, and all persons named in the Acknowledgements section have given written permission to be named in the manuscript.

✔ Additional information (failure to provide this information at submission may lead to delays in processing):

- Name, email, postal address, telephone number, and VAT number (where applicable; for registered EU companies) for financial correspondence;
- Details of and reasons for any specific publication deadline;
- Information on where you heard about the journal;
- The email address of anyone, other than the corresponding author, who should receive manuscript correspondence throughout the publication process;
- Details of any digital features;
- Details of the ethics statements applicable to the study;
- If the trial was registered, please include details of the trial registration including a clinical trials number, beneath the abstract (e.g. *Trial registration: ClinicalTrials.gov identifier, NCT12345678).* For trials that were registered retrospectively, please also include the date of registration and the words “retrospectively registered” beneath the abstract. Trial registration is not mandatory; however, we strongly encourage prospective registration of clinical trials.
- *Advances in Therapy ONLY:* Whether you require the article to be published open access; all other journals in the portfolio are fully open access.

✔ Details (name, affiliation, and email address) of up to three suggested reviewers for your submission (optional). Recommended reviewers should not be from any of the authors' affiliations or institutions or have any potential conflicts of interests that may affect their ability to provide an unbiased review of the article. Please note that, although your help is appreciated and may speed up the selection of appropriate reviewers, the Editorial Team reserves the right to select reviewers.

File Checklist

The following files are needed during the submission process. Each item in the checklist should be saved as a separate file.

- ✔ Manuscript including title page, abstract, keywords, 4-5 key summary points, main text, acknowledgements, references, tables, figure legends, and line numbers;
- ✔ Figures (each figure should be submitted as a separate file either as a JPG or TIFF file);
- ✔ Any supplementary material (optional);
- ✔ Any digital features (optional).

PRESUBMISSION ENQUIRIES

Please contact the journal's Editorial Team to address any queries you may have prior to, during, or after manuscript submission. In particular, contact the Editorial Team regarding enquiries for manuscripts with specific, important publication deadlines, or in instances where you are unsure of a manuscript's suitability for the journal.

For enquiries specifically related to one of the Adis Rapid+ journals, you are also welcome to contact the Managing Editor directly (see links to journal-specific websites at the beginning of this document).

ARTICLE TYPES

The journals publish a variety of article types. All article types described below are subject to peer review.

Original Research/Brief Reports

We recommend that manuscripts reporting on original research conform to the CONSORT guidelines, whenever possible, although this is not mandatory. Research articles are welcome across the clinical research pathway (including post-marketing research, observational studies, and health economics and outcomes research).

As a guide, Original Research articles should be around, but not limited to, 4000 words.

Brief Reports describing a clinical study, or new insights into clinical management, diagnosis, or treatment are welcome. Brief Reports describe studies that are smaller in scale and patient numbers, and may report limited pilot data that warrant the need for further investigation. Authors are encouraged to use these sections when submitting the manuscript: Introduction (including the research hypothesis), Methods, Results, Discussion, and Conclusion. As a guide, Brief Reports should be around, but not limited to, 2000-3000 words.

The abstract and main text of all Original Research articles and Brief Reports should be structured as follows: Introduction (including the research hypothesis), Methods, Results, Discussion, Conclusion.

For all studies involving human participants, we encourage all authors to follow the Sex and Gender Equity in Research (SAGER) guidelines, and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully to prevent confusion between both terms. Article titles and/or abstracts should indicate what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We recommend that authors consult the full guidelines before submission.

Reviews

Comprehensive reviews of a specific drug, device, or particular area of interest are welcome. If conducting a review of the current literature, please provide details of the databases searched, the dates to which the search is limited, and search terms. Systematic reviews and meta-analyses should conform to the PRISMA guidelines, although this is not mandatory. The abstract and main text of systematic reviews and meta-analyses should be structured as follows: Introduction, Methods, Results, Discussion, Conclusion. If submitting a Review, please indicate in the title the format of the Review (e.g. systematic, narrative). As a guide, Reviews should be around, but not limited to, 8000-10,000 words.

Case Series

Manuscripts describing a number of interesting, unusual, or novel individual medical cases focusing on the same indication are welcome in the form of a Case Series. Manuscripts are encouraged to follow the CARE guidelines for reporting cases, although this is not mandatory. Authors should make clear the importance of their particular cases, summarise previous research in the condition, explain the implications for future therapy, and how the Case Series adds to the medical literature. Manuscripts must meet at least one of the following criteria to be eligible for consideration:

- Unreported or unusual side effects or adverse interactions involving medications;
- Unexpected or unusual presentations of a disease;
- New associations or variations in disease processes;
- Presentations, diagnoses, and/or management of new and emerging diseases;
- An unexpected association between diseases or symptoms;
- An unexpected event in the course of observing or treating a patient;
- Findings that shed new light on the possible pathogenesis of a disease or an adverse effect.

Case Series should have the following structure: Abstract; Introduction (including a summary of why the cases are unique/important with reference to relevant medical literature); Case presentations (including patient information, clinical findings, timeline, diagnostic assessment, therapeutic intervention, follow-up, and outcomes, etc.); Discussion; Conclusion(s) (including the primary “take-away” lessons from the case series); Acknowledgements; References. As a guide, case series should be around, but not limited to, 3000 words.

Consent to publish must be obtained from the patients or the patients' parents, relatives, guardian, etc. A consent form can be requested from the Editorial Team. Note: We do not require this form as part of the submission, but it must be declared in the manuscript that written informed consent for the publication of the patients' clinical details was obtained and that a copy of the consent form is available for review by the Editor.

Case Reports

Please note that *Advances in Therapy* does not accept Case Reports.

All other Adis Rapid+ journals will consider unique individual Case Reports but these should meet the same eligibility criteria and ethical requirements regarding consent given above for Case Series. Manuscripts are encouraged to follow the CARE guidelines for reporting cases.

As a guide, Case Reports should be around, but not limited to 2000 words.

Commentaries

Commentary articles are designed to allow an author to put a particular topic/research into their own perspective, drawing on their own experiences and insights, and backing up their arguments with existing evidence. There is no mandatory structure and authors are encouraged to structure their Commentary in a way that best suits their voice. As a guide, Commentaries should be around, but not limited to, 2000-3000 words.

Patient/Physician Perspectives

These commentary-style articles are designed to highlight patient experiences and raise healthcare professional awareness of the patient perspective and best practices for patient-centricity. The first half of the piece is written by a patient, describing their experience of living with a particular condition. For example, day-to-day experiences, the journey to a correct diagnosis, response to treatment, psychosocial aspects of the condition, side effect management, quality of life issues, or anything that is important and relevant to them. This section may also be written (or co-written) by the carer or guardian of the patient. The second half of the article is written by an expert physician or any other healthcare practitioner(s). This would usually be the patient's own treating physician; however, if this is not possible, another healthcare practitioner who is familiar with the condition could write the accompanying perspective. This section may also be written (or co-written) by other healthcare professionals and should be underpinned with evidence referenced from available literature. As indicated above, these articles can include multiple perspectives and are not limited to patients/physicians. As a guide, Patient/Physician Perspectives should be around, but not limited to 2000-3000 words.

Physicians should discuss with their patients the potential consequences of identifiable personal and medical information being published open access, so that patients can choose in a fully informed way whether to co-author in an open access publication. If requested, patients/caregivers/parents can choose to remain anonymous.

An example of a Patient/Physician Perspective article can be found below:
https://link.springer.com/article/10.1007/s40487-020-00132-2

Podcast Articles

Podcast articles follow a commentary style of publication, and typically feature a Q&A expert discussion with the author (or authors) around a topic of clinical interest, such as clinical data or real-life expert experience and opinions.

Adis Podcasts are published on SpringerLink. If open access, the podcast audio will also be published on Figshare and a number of popular podcast platforms (including Apple, Spotify, Deezer, and GooglePlay). Podcast articles are also indexed on PubMed.

The SpringerLink-hosted version consists of the audio podcast, along with the verbatim transcript. This transcript is typeset and published as a regular article within the journal with a DOI. Abstracts for Podcast articles are optional.

The journal strongly encourages authors to contact the relevant journal with a presubmission enquiry before initiating a Podcast article, and to read the Adis "*Guidelines for Digital Features and Plain Language Summaries*", which can be found under the submission guidelines on the relevant journal's homepage.

An example of a Podcast article is provided below:
https://link.springer.com/article/10.1007/s40120-021-00266-z

Trial Designs/Study Protocols

Study Protocols for any proposed or ongoing trials may also be submitted. All protocols will undergo peer review prior to publication. It is recommended that the article be structured as follows: Abstract (summarising the introduction [background/objectives], methods, planned outcomes); Introduction (background, objectives, trial design); Methods (study design, sample selection, measurements, planned outcomes, data collection, data analysis); Strengths and Limitations; Ethics; and Dissemination. For further information on protocol reporting, please read the SPIRIT statement. As a guide, Study Protocols should be around, but not limited to, 2000-3000 words.

Study Protocols are not only limited to clinical trials; they can also apply to real-world/observational studies or other types of future planned research.

Publication of original research relating to study protocols that have already been published in an Adis Rapid+ journal is entitled to a 20% discount on the journal's Rapid Service Fee. This should be highlighted in your cover letter when submitting.

Practical Approaches

Practical Approach articles intend to provide innovative and novel evidence-based practical guidance on difficult clinical management issues. Each article aims to provide a succinct and

accessible overview of a key topic for the broad range of healthcare professionals working with patients, including nurses and primary care physicians, and encompassing engaged patients and their caregivers where appropriate. The objective of these articles is to concisely review the most recent evidence relating to a clinical care situation and place this into a practical context. The use of flow charts, demonstrative videos, and visual material is encouraged in these articles to help readers digest the key information. As a guide, Practical Approach articles should be around, but not limited to, 2000 words.

Guidelines

Guidelines provide a comprehensive guide to the optimum management of a disease, disorder, or situation which highlight clinically relevant considerations and recommendations. These articles may be affiliated with societies but this is not a requirement. If guidelines are from a particular society, this should be highlighted in the article title. If included on the title page, the member's names will be included as collaborators on PubMed. For Guidelines, we also ask that the following disclaimer is included within the acknowledgements section of the article: "Springer Healthcare is not responsible for the validity of guidelines it publishes.". As a guide, Guidelines should be around, but not limited to, 10,000-15,000 words.

Letters to the Editor

Letters will be considered on a case-by-case basis and reviewed by the journal's Editorial Board. Letters should comment on a recently published article in the journal and are limited to one comment and one response by the authors of the original paper, should they wish to respond. As a guide, Letters to the Editor should be around, but not limited to, 1000 words.

TOPICAL COLLECTIONS AND SUPPLEMENTS

Adis Rapid+ journals welcome supplements. Material appropriate for supplements includes: sponsored meeting proceedings, roundtable discussions, workshop reports, case series, and collections of articles on the same topic.

The journals also support topical collections, which aim to collate articles on a certain topic, making them easily accessible to interested readers. Articles in a topical collection are published in a standard journal issue; however, they are also accessible through a dedicated topical collection page on the website.

Proposals for supplements and topical collections are welcome and should be addressed to journal specific Managing Editors (see list of journal specific links at the beginning of this document).

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Adis Rapid+ journals can publish a range of digital features alongside articles (including videos, video abstracts, slide decks, audio features, infographics, and more). These features are designed to increase visibility, readership, and the educational value of the article. As all digital features are peer reviewed to the same high standard as the article itself, the journal prefers submission of such content at the same time as the article. However, digital features can be submitted retrospectively.

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fee will be issued through a separate invoice. For full pricing information, please visit the journal websites.

MANUSCRIPT STRUCTURE

All articles should follow the guidelines below for the Title page, Abstract, Keywords, Key summary points, Introduction, Discussion, Conclusion, Acknowledgements, References, Figures, Tables, and Supplementary material. Original Research articles should also follow the guidelines for Methods and Results. Abstracts and Key summary points are not mandatory for Letters, Commentaries and Editorials and authors can use their discretion for the structure and headings used in these article types. Submissions are encouraged to conform to the standards outlined in the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals," prepared by the ICMJE.

General

Line Numbers: To facilitate the review process, we request that authors submit a line-numbered version of their manuscript.

Drug Names: When drugs are mentioned, the international (generic) name should be used. If the proprietary name is required, for example to distinguish between formulations, the manufacturer should be stated in full after the first mention of the proprietary name and the unregistered (™) or registered (®) trademark symbol should be used. The symbol does not need to be used subsequent to the first mention. The source of any new and experimental preparation should also be given.

Spelling, Abbreviations, Nomenclature, and Units: Authors may choose US or UK English spelling. However, this must be consistent throughout the manuscript. All standard and nonstandard abbreviations in the text must be defined at first mention and used consistently thereafter. Symbols should not be used unless first explained in the text (reference guide: *Units, Symbols and Abbreviations*, Royal Society of Medicine, London). Highly sophisticated, specialist terms should either be defined or avoided. Intelligibility is a major aim of the journals. For substances, materials, and instruments, the correct designation and the manufacturer's name should be given. The city and country of the manufacturer should also be included. For units of measure (International System of Units) SI units should be used throughout, except where non-SI units are more common.

Title Page

The title page should include the following elements:

- *Title*: Should capture the essence of the manuscript in no more than 20 words (within reason). The title should be specific enough for electronic retrieval and searches. Where relevant, the title should include the drug name, indication, and study design. If appropriate, the country- or population-specific (e.g. pediatric) nature of the study should also be clear from the title. Where possible use generic drug names.

- *Author Details*: The name(s) of all authors and their institutional affiliation(s) and address(es). It is recommended that authors adhere to the guidelines for authorship that are

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