UNIVERSIDADE DE LISBOA
Faculdade de Medicina


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Orientador(es): Prof. Doutor Joaquim José Coutinho Ferreira

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Tese especialmente elaborada para obtenção do grau de Doutor em Neurociências

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2020

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**DEDICATÓRIA**

*Para a minha amada Melissa*

*Meu anjo;*
*Teu sorriso espelha o sol e aquece;*
*Teu colo, como um ninho plumas, conforta;*
*Tuas palavras sábias iluminam e guiam;*
*Tua doçura, maior que o melaço, encanta;*
*Tua fé, inamovível, norteia;*
*Teus modelos, bondosos e corretos, as crianças esculpem;*
*Teu zelo, inestimável, cuida;*
*Teu carinho, meigo, alegra;*
*teu Herte, maroto, provoca;*
*Mas é teu Amor, infinito, que transborda por todos os teus poros,*
*Que fazem que eu seja grato por ter-te a ti.*

*Rodrigo*

## CONTENTS

**ABSTRACT**

**Background**

Randomized controlled trials (RCTs) are the gold standard studies to evaluate the efficacy of therapeutic interventions. However, performing RCTs in surgical disciplines, including neurosurgery, faces several specific challenges such as recruitment difficulties, surgical selection bias, inclusion of an appropriate control group, definition of clinically relevant outcomes and perceived lack of equipoise. Therefore, little is known about the number of published RCTs in neurosurgery, how they are performed and reported and their scientific quality. This, in turn, raises questions regarding the sources of knowledge that currently support clinical decision-making by neurosurgeons.

Therefore, the present investigation aims to explore the current scenario of RCTs in neurosurgery and sources of knowledge used for clinical decision-making.

**Hypothesis and significance:** Given the previously reported difficulties inherent to design and perform RCTs in neurosurgery, it is hypothesized that RCTs in this field are low in number and of suboptimal quality, leading neurosurgeons to use other sources of knowledge for clinical decision-making. The current research aims to better understand the current scenario and ultimately contribute for better decision-making in this field.

**Aims and methodological approach:** This research comprised four aims. Aim 1. To investigate the attitudes of Brazilian neurosurgeons in terms of access and use of different types of scientific information for clinical decision-making, by means of a cross-sectional survey that was sent to all members of the Sociedade Brasileira de Neurocirurgia. The answers were analyzed descriptively and comparisons were made among subgroups of practice place and time. Aim 2. To evaluate how easy it is to have access to published RCTs in neurosurgery using several electronic search strategies applied to commonly used databases. This was achieved by carrying out open searches on PubMed, the Cochrane Library and the Centre for Reviews and Dissemination, an advanced search on PubMed based on clinical entity-related keywords, and hand-searches on the reference list of the identified RCTs. The outcomes were the sensitivity and specificity calculated for the open keyword searches on PubMed, the Cochrane Library and the CRD database and for the Cochrane's HSSS, based on the total number of the identified RCTs. Aim 3. To investigate the scientific quality of RCTs in neurosurgery through a systematic review performed in all identified randomized trials with two or more comparative groups and at least one neurosurgical

intervention. Study design and other methodological aspects were analyzed. The quality of included RCTs was assessed using the Cochrane Risk of Bias tool. Aim 4. To investigate how feasible it is to use sham controls in neurosurgery RCTs by analyzing the frequency, type and indication of used sham interventions.

**Results:** Aim 1: The survey's response rate was 32%. Among the respondents, 53% had more than 10 years experience, 67% worked in public hospitals, 34% performed spine and 30% brain tumor surgeries. Therapeutic decisions were based mostly on internship learning (54%) and personal professional experience (52%). Most common information sources were scientific abstracts (53%) and the internet (47%). 89% believed Evidence-Based Medicine to be relevant, 93% believed protocols or guidelines were necessary and 74% subscribed to a medical journal. Nonetheless only 43% had protocols implemented in their services, 93% highly valued a surgeonś personal experience and 63% showed little familiarity with the interpretation of scientific concepts in the literature. 83% were willing to try an innovative treatment alternative if it showed improvement of the outcomes and reduction of severe complications.

Aim 2: A total of 1102 RCTs identified through combined search strategies. PubMed open search yielded 4660 articles, among which 365 were RCTs (sensitivity: 33.1%; specificity: 7.8%). Cochrane open search yielded 621 among which 36 were RCTs (sensitivity: 3.2%; specificity:5.8%) and CRD open search returned 78 articles, among which 4 were RCTs (sensitivity: 0.4% sensitivity; specificity: 5.1%). The Cochrane HSSS retrieved 10702 results, among which 340 were RCTs (sensitivity: 30.9%; specificity: 3.2%).

Aim 3: RCTs in neurosurgery were found to lack quality, as most lacked information on study design (93.6%), randomization method (59.9%), blinding (59.8%), and data analysis (76.3%). Although the overall risk of bias decreased over time, 25.5% of the RCTs published between 2010 and 2013 lacked a clear risk of bias classification due to insufficient critical information. The methodological aspects more frequently classified with high risk of bias were "blinding of participants and personnel" (21.2%) and "incomplete outcome information" (28.8%).

Aim 4: From the 1102 identified RCTs, 82 (7,4%) used sham interventions. The most common indication was pain treatment (67,1%), followed by the treatment of movement disorders and other clinical problems (18,3%) and brain injuries (12,2%). The most used sham interventions were saline injections, both in the spine (31,7%) and peripheral nerves (10,9%), followed by cranial surgery (26,8%), spine surgery (15,8%) and insertion of probes or catheters for sham lesions (14,6%).

Most RCTs using sham interventions were double-blinded (76,5%), whereas 9,9% were single-blinded, and 13,6% did not report the type of blinding.

**Discussion:** Although RCTs constitute the highest level of evidence, in the field of neurosurgery they are currently not the main source of knowledge underlying therapeutic decision-making, as most neurosurgeons, particularly those with over 10 years of experience, prefer to rely on their own expertise. Additionally, RCTs in neurosurgery are not easily accessible through commonly used search strategies applied to electronic databases, which is mostly due to poor quality of reporting and indexing.

Moreover, published RCTs in neurosurgery lack quality in terms of experimental methodology, and they are poorly reported, with missing information on several critical design aspects. Although the inclusion of sham procedures in neurosurgical RCTs is feasible, very few include such procedures, which limits the clinical relevance of the estimated effects. Our results highlight an urgent need to improve the methodological quality, reporting and indexing of RCTs in neurosurgery, which may be achieved through the implementation of reporting guidelines, adequate training and rigorous peer-review.

**RESUMO**

**Contexto**

Os ensaios clínicos randomizados (RCTs) são os estudos mais adequados para avaliar a eficácia de novas terapêuticas. Contudo, nas disciplinas cirúrgicas incluindo a neurocirurgia, a sua realização está limitada por aspetos específicos como a dificuldade de recrutamento de participantes, bias na seleção dos procedimentos cirúrgicos, inclusão de um grupo controlo adequado, definição de outcomes clinicamente relevantes e falta de equipoise. Como tal, pouco se sabe acerca do número de RCTs publicados em neurocirurgia e da sua qualidade científica. Isto, por sua vez, levanta questões acerca das fontes de conhecimento utilizadas para a tomada de decisões clínicas em neurocirurgia.

Assim, a investigação realizada no âmbito desta tese visou perceber o presente cenário dos RCTs realizados em neurocirurgia, bem como das fontes de informação científica utilizadas como base para as decisões clínicas.

**Hipótese e Relevância:** Tendo em conta as dificuldades inerentes à conceção e realização de ensaios clínicos em neurocirurgia, é formulada a hipótese de que o número de RCTs realizado nesta área seja baixo, e que a sua qualidade seja sub-ótima, levando os neurocirurgiões a recorrer a outras fontes de evidência como suporte para as suas decisões clínicas. A presente investigação tem como objetivo compreender o presente cenário e contribuir para melhorar a tomada de decisões clínicas nesta área.

**Objetivos e Metodologia:** Esta investigação teve quatro objetivos. Objetivo 1. Investigar as fontes de conhecimento utilizadas por neurocirurgiões Brasileiros para basear as suas decisões clínicas, através de um inquérito online que foi enviado por correio eletrónico a todos os membros da Sociedade Brasileira de Neurocirurgia. As respostas foram analisadas descritivamente e realizaram-se comparações entre subgrupos relativos a local de trabalho e tempo de experiência. Objetivo 2. Investigar a acessibilidade dos RCTs publicados em neurocirurgia através de estratégias de busca aplicadas às principais bases de dados, utilizando diferentes estratégias de busca como a procura por palavras-chave realizadas nas bases de dados PubMed, Cochrane Library e Centre for Reviews and Dissemination, busca avançada na PubMed utilizando palavras-chave relacionadas com entidades clínicas e buscas manuais nas listas de referências dos RCTs identificados. Os resultados avaliados foram a sensibilidade e especificidade, calculadas para cada busca por palavra-chave, busca avançada e para a HSSS

da Cochrane, com base no número total de RCTs identificados. Objetivo 3. Investigar a qualidade dos RCTs publicados em neurocirurgia foi investigada através de uma revisão sistemática de todos os RCTs identificados, que incluíssem dois ou mais grupos comparativos e pelo menos uma intervenção neurocirúrgica. O desenho experimental e outros aspectos metodológicos foram analisados, e a qualidade dos RCTs foi quantificada utilizando a ferramenta Risk of Bias da Cochrane. Objetivo 4. A exequibilidade da inclusão de procedimentos sham nos RCTs em neurocirurgia foi investigada através da análise de todos os RCTs com dois ou mais grupos comparativos e pelo menos uma intervenção neurocirúrgica. Foi determinada a frequência de utilização de procedimentos sham como controle, assim como o tipo e indicação da intervenção. Adicionalmente, todos os RCTs que incluíram procedimentos sham como controle foram caracterizados em termos de design experimental e de Risk of Bias.

**Resultados**: Objetivo 1. O inquérito online obteve 32% de respostas. Entre os respondentes, 53% tinham mais de 10 anos de experiência, 67% trabalhavam em hospitais públicos, 34% realizavam cirurgias à coluna vertebral e 30% realizavam cirurgias a tumores cerebrais. As decisões terapêuticas baseavam-se principalmente na aprendizagem adquirida em estágios (54%) e na experiência profissional (52%). As fontes de informação mais comummente utilizadas foram os resumos científicos (53%) e a internet (47%). 89% dos respondentes reconhecia a relevância da medicina baseada na evidência, 93% considerava necessária a existência de protocolos e guidelines e 74% assinava uma revista médica. Apesar disso, apenas 43% tinha protocolos implementados no seu serviço, 93% atribuía um valor elevado à experiência profissional e 63% teve dificuldade na interpretação dos conceitos científicos presentes na literatura. 83% estariam dispostos a experimentar novos tratamentos, desde que levassem a melhorias de resultados e redução de complicações severa. Objetivo 2. A utilização combinada de várias estratégias de busca identificou um total de 1102 RCTs em neurocirurgia. Buscas abertas identificaram 4660 artigos na PubMed, entre os quais 365 RCTs (sensibilidade: 33.1%; especificidade: 7.8%), 621 artigos na Cochrane, dos quais 36 eram RCTs (sensibilidade: 3.2%; especificidade: 5.8%) e 78 artigos na CRD, dos quais 4 eram RCTs (sensibilidade: 0.4%; especificidade: 5.1%). A HSSS da Cochrane identificou 10702 artigos, dos quais 340 eram RCTs (sensibilidade: 30.9%; especificidade: 3.2%). Objetivo 3. A revisão sistemática revelou que os RCTs publicados em neurocirurgia têm qualidade sub-óptima, uma vez que a maioria não reportou informação relativa ao desenho experimental (93,6%), método de randomização (59,9%), blinding (59.8%), e tipo de análise de dados

efectuada (76.3%). Embora o Risk of Bias geral tenha diminuído ao longo do tempo, 25.5% dos RCTs publicados entre 2010 e 2013 não permitiu uma classificação clara do Risk of Bias, devido ao reporte insuficiente de informação crítica. Os aspectos metodológicos mais frequentemente classificados com Risk of Bias alto foram "blinding de participantes e pessoal" (21.2%) e "informação incompleta sobre outcomes" (28.8%). Objetivo 4. Entre of 1102 RCTs identificados, apenas 82 (7.4%) incluíram procedimentos sham. A indicação mais comum foi o tratamento da dor (67.1%), seguida do tratamento de doenças do movimento e outros problemas clínicos (18.3%) e lesões cerebrais (12.2%). Os procedimentos sham mais utilizados foram injeções de salina na coluna vertebral (31,7%) e nervos periféricos (10.9%), seguidas de cirurgia craniana (26.8%), cirurgia vertebral (15.8%) e inserção de sondas ou cateteres para provocar lesões sham (14.6%).

A maioria dos RCTs que incluíram procedimentos sham utilizaram double-blinding (76.5%), enquanto 9.9% utilizaram single-blinding e 13,6% não reportou o tipo de blinding utilizado.

**Discussão:** Embora os RCTs constituam o mais elevado nível de evidência, atualmente na área da neurocirurgia não são a principal fonte de conhecimento utilizada para suportar as decisões terapêuticas. A maioria dos neurocirurgiões, e particularmente os que têm mais de 10 anos de experiência, preferem utilizar o seu próprio conhecimento.

Além disso, os RCTs em neurocirurgia não são facilmente obtidos através das buscas mais utilizadas nas principais bases de dados, o que se deve principalmente a mau reporte e indexação. Adicionalmente, os RCTs publicados em neurocirurgia têm pouca qualidade em termos de metodologia experimental e reporte, omitindo frequentemente informação em vários aspectos críticos.

A inclusão de procedimentos sham nos RCTs em neurocirurgia é exequível. Apesar disso, muito poucos incluem esses procedimentos, o que limita a relevância clínica dos efeitos estimados.

Os resultados desta tese salientam uma necessidade urgente de melhorar a qualidade dos RCTs em neurocirurgia, relativamente à metodologia, reporte e indexação. Esta melhoria poderá ser obtida através da implementação de guidelines de reporte, formação adequada e mais rigor na revisão por pares.

**LIST OF PUBLICATIONS IN SUPPORT OF THIS THESIS**

1. Gorayeb RP, Forjaz MJ, Gonçalves Ferreira A, Ferreira J. Information Sources and Decision-Making in Neurosurgery: Results of a Survey of Members of the Brazilian Neurosurgery Society. 2018. Arq. Bras. Neurocir. 37(02): 081-087. DOI: 10.1055/s-0038-1656716

2. Gorayeb RP, Forjaz MJ, Ferreira AG, Duarte GNS, Machado T, Ferreira JJ. Electronic search strategies fail to identify randomized controlled trials (RCTs) in neurosurgery. 2019. Clin Neurol Neurosurg. 184:105446. doi: 10.1016/j.clineuro.2019.105446.

3. Gorayeb RP, Forjaz MJ, Ferreira AG, Ferreira JJ. Use of Sham Interventions in Randomized Controlled Trials in Neurosurgery. 2020. J Neurol Surg A Cent Eur Neurosurg. doi: 10.1055/s-0040-1709161.

Submitted manuscript

4. Gorayeb RP, Forjaz MJ, Ferreira AG, Ferreira JJ. Low quality of randomized controlled trials in neurosurgery: results from a critical appraisal of 1102 RCTs
Br J Neurosurg (submitted 25/03/2019, under peer review em 31/05/20202)

*ABREVIATURAS*

**BNS -** Brazilian Neurosurgery Society

**CI -** Confidence Interval

**CONSORT -** Consolidated Standards of Reporting Trials

**CRD -** Centre for Reviews and Dissemination

**EBM -** Evidence Based Medicine

**EMBASE -** Excerpta Medica Database

**EUDRACT -** European Union Drug Regulating Authorities Clinical Trials

**GRADE -** Grades of Recommendation, Assessment, Development and Evaluation

**HSSS -** High Sensitivity Search Strategies

**IBM -** International Business Machines, Co

**ICMJE -** International Committee of Medical Journal Editors

**ICTPR -** International Clinical Trials Registry Platform

**IDET -** intradiscal electrothermal therapy

**JJF -** Joaquim José Ferreira

**MA -** Meta-analysis

**PUBMED -** Public Medline

**RCTs -** Randomized Controlled Trials

**RG -** Rodrigo Gorayeb

**SBN -** Sociedade Brasileira de Neurocirurgia

**SR -** Systematic Reviews

## *CHAPTER 1. INTRODUCTION*

### Neurosurgery

Neurosurgery is the medical discipline that diagnoses and treats diseases of the brain, spinal cord, peripheral nerves and the respective supporting vasculature, both in pediatric and adult patients. It is a holistic discipline focusing on a complete system, rather than specific body regions. Although it is mostly a surgical discipline, neurosurgery requires considerable knowledge on related medical fields such as neurology, critical care, trauma and radiology.
Conditions that fall within the scope of neurosurgery include all pathological processes that may modify the function or activity of the central nervous system, such as congenital disorders, trauma, tumors, vascular anomalies, seizures, infections and aging-related disorders such as stroke, functional disorders and degenerative conditions of the spine (Cohen-Gadol, 2016).

### Therapeutic interventions in neurosurgery

Therapeutic interventions in neurosurgery can be surgical or non-surgical, and those can be arbitrarily separated by guiding institutions. The American Board of Neurological Surgery, for example, states that  Surgical interventions involve physical changes to body tissues and organs through manual procedures such as cutting, abrading, suturing and laser use. As for its types, surgical interventions and related image use and interpretation include endovascular surgery, functional and restorative surgery, stereotactic radiosurgery and spinal fusion. Non-surgical interventions encompass diagnostic, preventive and therapeutic procedures (including image interpretation) such as, but not limited to, those used in neurocritical intensive care and rehabilitation. Other authors vary only slightly in their interpretation, overall stating the same principles (Cook, 2009; ABNS,2020).

Hughey et al. (2010) classified surgical interventions in neurosurgery into 8 mutually exclusive categories: craniotomy/craniectomy, subdivided into tumor removal, vascular surgery, and those for other purposes; endovascular procedures, subdivided into intracranial

and head and neck region; deep brain stimulation, shunts (ventricular and thecal), and spinal fusion.

**Randomized controlled trials in neurosurgery**

Randomized controlled trials (RCTs) were developed in the twentieth century as mathematical models to describe the complex responses of the human body to therapeutic interventions (Meldrum, 2000). Such models were developed by medical researchers and statisticians to compare two or more therapeutic regimens under controlled conditions. One of the compared regimens can be a traditional treatment, a placebo, or the exclusion of an active treatment. RCTs are based on the statistical analysis of the possibility of error.

This recognized methodology comprises three fundamental features: (1) inclusion of control groups, (2) use of randomization, and (3) blinding (Meldrum, 2000) and is currently considered as the gold standard to evaluate the effectiveness of therapeutic interventions, for being the most scientifically rigorous method for hypothesis testing (Akobeng, 2005).

Despite their scientific rigor, RCTs are not a straightforward solution; on the one hand, comparing groups often means that one set of subjects will receive a less effective treatment, or possibly none at all, which may constitute an ethical issue. Randomization can be rendered ethical by the presence of equipoise, which implies that a subject may be enrolled in an RCT only if there is true uncertainty about which of the treatment arms is more likely to benefit him/her (Fries and Krishnan, 2004). On the other hand, RCT design is limited by constraints of cost, time, and personnel, which may require assigning certain subjects to certain treatments, specifying outcome measures and criteria, and setting limits to the duration of treatment and follow-up (Meldrum 2000).

Other limitations of RCTs have been pointed out; despite their high internal validity, RCTs lack external validity, as their results cannot always be generalized outside the study population (Frieden, 2017; Mulder et al., 2018). Usually their duration and sample size are not sufficient to assess the duration of treatment effects or to detect rare but serious adverse effects (some of which occur after marketing surveillance) (Mansouri et al., 2016). They have increasingly high cost and time constraints, which may lead to the use of surrogate outcomes

that may not correlate sufficiently with the real clinical outcome (Lewis and Warlow, 2004). While the selection of high-risk groups increases the likelihood of having an adequate number of end-points, these groups are not always relevant to broader target populations.

RCTs take years to plan, implement and analyze (Frieden, 2017) and are often limited by common sources of bias such as poor allocation concealment, imbalance of baseline prognostic variables, lack or correct blinding, missing data, lack of intention-to-treat analysis, inadequate analysis of deaths (sometimes included as a good outcome), and competing interests (Lewis and Warlow, 2004).

In the specific case of neurosurgery, RCTs are considered challenging to perform due to the difficulties posed by patient inclusion, surgical selection bias, inclusion of an appropriate control group, definition of clinically relevant outcomes, perceived lack of equipoise, and provision of a conclusive answer to the initial question (EC/IC Bypass Study Group, 1985; Mohr et al., 2014). As a consequence of these limitations, most innovation in neurosurgery occurs without formalized oversight, which has been justified on the grounds of surgery's unique nature and characteristics—referred to as "surgical exceptionalism" (Martin 2019).

Therefore, most surgical research takes the form of retrospective case series, which often include a small number of patients (Panesar et al., 2006; Al-Harbi et al., 2009) Surgical treatments are therefore less likely to be based on evidence from RCTs than medical therapies. Moreover, the challenges inherent to neurosurgical RCTs may lead to a faulty design and methodology, thereby generating misleading results (Farrokhyar, 2010). Additionally, the internal validity of surgical trials is often lower than that of drug trials because the outcomes are dependent on the characteristics of the participating surgeons and settings (Farrokhyar, 2010).

Other pertinent issues, such as the concept of the technical learning curve, surgical intervention standardization and patient recruitment are also genuine concerns with neurosurgical RCTs (Mansouri et al., 2016).

Standardizing surgical interventions is a difficult task and most innovative surgical procedures are introduced in the form of case-series and adopted into practice without a proper evaluation (Farrokhyar, 2010). Most neurosurgical procedures are the result of continuous improvement and evolution of existing practices and are rarely compared with non-operative management.

**Sources of knowledge in neurosurgery**

Evidence-based medicine (EBM) is the "*conscientious, explicit, and judicious use of the current best evidence to make decisions about the care of individual patients, thereby integrating individual clinical expertise with the best available external clinical evidence from systematic research*" (Sackett et al., 1996). It focuses on educating front-line clinicians to assess the credibility of research evidence, understand the results of clinical studies, and determine how best to apply the results to their everyday practice (Djulbegovic and Guyatt, 2017).

Several investigators have provided examples of biased research leading to suboptimal medical practice, lamenting the "scandal of poor medical research" (Altman, 1994) and claiming that "most research finding[s] are false" (Ioannidis, 2005). Estimates suggest that 50% of research effort is wasted at each stage of generation and reporting of research, resulting in more than 85% of total research wasted (Macleod et al., 2014).

In response, EBM has developed schemas to assess evidence quality, reflecting the first EBM epistemological principle: "*the higher the quality of evidence, the closer to the truth are estimates of diagnostic test properties, prognosis, and the effects of health interventions*" (Djulbegovic and Guyatt, 2017).

Evidence-based medicine is currently state of the art also within neurosurgery, where evidence-based neurosurgery (EBN) refers to "*the application of clinical neuroepidemiology to the care of patients with neurosurgical problems*" (Esene et al., 2016). EBN integrates clinical/surgical expertise and judgment, patient preferences and values, clinical circumstances, and the best available research evidence to provide a framework for patient care (Sackett et al., 1996; Yarascavitch et al., 2012) and has therefore become one of the pillars of modern neurosurgery.

This raises the question of what constitutes good scientific evidence.

Initially, evidence hierarchies were based on the design of clinical studies, with RCTs being considered superior to observational studies in the estimation of treatment effects (Djulbegovic and Guyatt, 2017). However, as it was noted that RCTs can also be biased and should not be automatically considered as high-quality evidence, changes were made to the original hierarchy of evidence, leading to over 100 systems available to rate the quality of medical research (West et al., 2002). The evaluation of each of those systems has provided inconsistent results (Juni et al., 1999; Atkins et al., 2004).

Awareness about the limitations of existing evidence hierarchies, together with the acknowledgement of the importance of processed evidence for ensuring evidence-based practice, and the related potential for practice guidelines to improve practice and outcomes, led to the development of a new approach to rate evidence quality and the strength of recommendations: the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system, which was first published in 2004. This system addresses all elements related to the credibility of the sources of knowledge: study design, risk of bias, precision, consistency, directness (applicability), publication bias, magnitude of effect, and dose-response gradients. In doing so, GRADE protects against both superficial assessment and unwarranted confidence in RCTs, as well as dogmatic decisions. Further, the rapidly increasing use of GRADE has resulted, and will increasingly result, in marked improvement in the quality of systematic reviews (Djulbegovic and Guyatt, 2017).

In many cases the best design for a particular question might not be an RCT, and an excellent, well-documented case report or a short series can raise questions and propose innovative approaches (Roitberg, 2012).

Nonetheless randomized controlled trials, as the pinnacle of EBM, must have their place in neurosurgery, designed very carefully and avoided when a good design turns out to be impractical or not feasible (Roitberg, 2012).

Systematic reviews, on the other hand are essential for developing clinical practice guidelines, for avoiding duplication of research efforts, and for helping inform design of new research studies (Djulbegovic and Guyatt, 2017).

## *CHAPTER 2. AIMS AND METHODOLOGICAL APPROACH*

The present thesis aimed to establish the state-of-the-art of clinical trials in neurosurgery, through the following aims:

Aim 1. Therapeutic decision-making: to identify the sources of knowledge most commonly used among neurosurgeons to support therapeutic decisions, as well as the perceived value of different sources of knowledge and the neurosurgeons' willingness to change their current practices, and its determining factors.

In September 2015, a questionnaire designed for the study was sent to the 2,400 members of the SBN using the SurveyMonkey (SurveyMonkey, San Mateo, CA, US) web tool. The questionnaire comprised 15 questions divided into 5 sections: 1) characterization of the participants; 2) perception of the research in neurosurgery and the decision-making process; 3) the way knowledge is obtained and transmitted; 4) how neurosurgeons handle new therapeutic alternatives; and 5) analysis of ethical considerations in the conception and implementation of clinical trials. The SBN sent a link to the online survey by email to all its members. Reminder emails were sent 3 times within 15 days. During these two weeks, a link and a request to fill out the questionnaire were also available on the SBN website (LINK https://docs.google.com/document/d/1zyhqagOEovwogIWQe5AJ6RPb8t1sGVh60AVMGDsxCrE/edit?usp=sharing).

Responses were collected anonymously, jointly analyzed, and only complete responses for each question were considered. The ethical committee of Faculdade de Medicina de Lisboa and the board of directors of the SBN were consulted for approval and saw no objections and deferred the need for a formal informed consent. A descriptive analysis of the response frequencies and the comparison between subgroups of duration and place of practice was performed using confidence intervals in comparative analysis and the Pearson chi-squared test was used for the correlations. For cases with 20% or more of the observations with a response frequency lower than 5, the Fisher exact test was used. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) version 20.0.

Aim 2. Accessibility: to evaluate how accessible are RCTs in neurosurgery when searching commonly used medical databases using different strategies.

Since clinical trials are the best studies to evaluate the efficacy of new treatments, it is crucial that they are easily accessible to medical professionals, thus enabling them to keep up-to-date with advances and making informed therapeutic decisions. The development of web tools and databases has considerably facilitated this process. However, there is currently no evidence that these tools are enough, allowing to identify all relevant publications, especially in the field of neurosurgery. As such, the second aim of this thesis was to investigate the sensitivity and specificity of commonly used search strategies to identify RCTs in neurosurgery published between 1960 and 2013.

The total number of RCTs in neurosurgery published between 1900 and December 31, 2013 was determined through a detailed search, which included the following steps: **a)** open electronic searches on PubMed, the Cochrane Library, and the Centre for Reviews and Dissemination (CRD) databases, using "RCTs" and "neurosurgery" as keywords; **b)** a PubMed search using keywords related to neurosurgical clinical entities (i.e., publication type = 'randomized controlled trial' AND (pathology subtype) AND date-publication = '1900/01/01':date-publication=2013/12/31), and **c)** hand-searches on the reference lists of the identified RCTs, systematic reviews and meta-analyses (Figure 1).

Duplications and abstracts were excluded from the total number of retrieved results, leading to the final list of published RCTs.

Once the final list was obtained, the search strategies most frequently applied to biomedical databases were assessed regarding the number of RCTs retrieved. These included the keyword searches applied to PubMed, the Cochrane library and the CRD databases, and the Cochrane's High Sensitivity Search Strategy applied to PubMed. Based on the findings of this assessment, the specificity and sensitivity of each of those search strategies were determined. Sensitivity (i.e., the ability to identify as many RCTs as possible) was calculated as follows: number of RCTs identified by each specific search strategy / total number of RCTs identified. Specificity (i.e., the ability to exclude as many irrelevant results as possible) was calculated as follows: number of RCTs identified by each of the specific search strategies / total number of articles returned by that particular search strategy.

Aim 3. Quality: to critically evaluate the identified RCTs regarding their methodological aspects and reporting quality. Since the results from the second aim of this thesis revealed that indexing influences how accessible RCTs are in the databases, the methodological and reporting quality of the identified RCTs was evaluated.

Following the search conducted in Aim 2, methodological information was collected from each article and entered into a data collection form and included the following methodological aspects: type of study design, inclusion criteria, study outcomes, sample size and its calculation method, dropouts and loss to follow-up, methods of randomization and blinding, statistical analyses, type of control, follow-up duration, reference to adverse events and description of interventions. All aspects were classified as either reported or not reported. In addition, the type of study design, type of outcome, sample size, dropouts and loss to follow-up, methods of randomization and blinding, type of statistical analyses, type of control and duration of follow-up were also registered. The publication dates were analyzed to investigate the changes on the number of RCTs published per year, and the studies were divided into 6 decades, to investigate changes on the Risk of Bias over time (1960-1969, 1970-1979, 1980-1989, 1990-1999, 2000-2009, 2010-2013). The information was extracted by one author (RG), and a second author (JJF) was consulted in cases of unclear information, or any doubt regarding the way to clarify the information.

Each RCT was classified according to the Cochrane Risk of Bias tool, as previously described (http://methods.cochrane.org/bias/assessing-risk-bias-included-studies). The following methodological aspects were classified with either “High”, “Low” or “Unclear” risk of bias: selection bias (i.e., random sequence generation and allocation concealment); performance bias (i.e., blinding of participants and personnel); detection bias (i.e., blinding of outcome assessment); attrition bias (i.e., occurrence of incomplete outcome data); reporting bias (i.e., selective outcome reporting); and other bias (i.e., other sources of bias, such as industry sponsorship). Subsequently, an overall risk of bias was determined for each RCT, which corresponded to the most prevalent classification. Trials with an equal number of methodological aspects classified with “High” and “Low” risk of bias, received an overall classification of “Medium” risk of bias. The proportion of RCTs classified with “High”, “Low” or “Unclear” risk of bias was calculated, both for each methodological aspect and overall. Additionally, the evolution of the risk of bias over time was determined. Data analyses were performed using the SPSS software (v22.0 - IBM). Unless stated otherwise, results are presented as numbers and percentages. The Spearman correlation was used to analyze the association between the reporting of critical information and the publication date, thus evaluating how reporting evolved over time. A level of $P < 0.05$ was considered statistically significant.

Aim 4. Use of a sham control: to determine the frequency of the use of sham procedures in neurosurgery RCTs.

The use of sham procedures in neurosurgery has been reported as rare and has raised ethical issues. To date, no studies have evaluated the frequency of the use of sham procedures, or the methodology of the studies that use them. Therefore, the fourth aim of the study was to determine the frequency of sham procedures in RCTs in neurosurgery, and to evaluate their methodological characteristics.

Included RCTs were identified by one of the authors (RG), who consulted a second author (JJF) for decision of unclear cases. Inclusion was based on the existence of a control group considered as a sham intervention either by the RCTs' authors, or by us.

The frequency of RCTs in neurosurgery using a sham control group was calculated. Analyzed information included the neurosurgical indication, type of sham intervention, and the most relevant methodological characteristics: type of blinding, type of outcome measured, number of patients included and lost (i.e., either drop-outs due to protocol violation, or participants lost to follow-up), and duration of follow-up. Each included RCT was classified with the Cochrane Risk of Bias tool, as described in Aim 3. The proportion of RCTs classified with "High", "Low" or "Unclear" risk of bias was calculated, both for each methodological aspect and overall.

## *CHAPTER 3. SOURCES OF KNOWLEDGE IN THERAPEUTIC DECISION MAKING*

**This section corresponds to the peer-reviewed manuscript with the reference:**

Gorayeb RP, Forjaz MJ, Ferreira AG, Ferreira JJ. Information Sources and Decision-Making in Neurosurgery: Results of a Survey to Members of the Brazilian Neurosurgery Society. 2018. Arq Bras Neurocir 37(02): 081-087. DOI: 10.1055/s-0038-1656716

**ABSTRACT**

**Background:** In all surgical disciplines including neurosurgery it is questioned the level of evidence supporting surgical practices and the mechanisms and adequacy of knowledge translation.

**Objectives:** To assess the Brazilian neurosurgeons' perception on the information sources and decision-making mechanisms regarding their medical practices.

**Methods:** An online questionnaire was sent to the 2400 members of the Brazilian Neurosurgical Society.

**Results:** 32% responded to the questionnaire, 53% had more than 10 years experience, 67% worked in public hospitals, 34% performed spine and 30% brain tumor surgeries. Therapeutic decisions were based mostly on internship learning (54%) and personal professional experience (52%). Most common information sources were scientific abstracts (53%) and the internet (47%). 89% believed Evidence-Based Medicine to be relevant, 93% believed protocols or guidelines were necessary and 74% subscribed to a medical journal. Nonetheless only 43% had protocols implemented in their services, 93% highly valued a surgeonś personal experience and 63% showed little familiarity with the interpretation of scientific concepts in the literature. 83% were willing to try an innovative treatment alternative if it showed improvement of the outcomes and reduction of severe complications.

**Conclusions:** The disparity in the collected information shows the need for implementing recommendations to improve the decision-making mechanisms.

## INTRODUCTION

Neurosurgical practices, as those from other medical specialties, depend on the diffusion, acceptance and establishment of specific technical procedures and clinical managements. This is done through the production of scientific data, ideally obtained through Randomized Controlled Trials (RCTs) or, in their absence, based on other information sources with the highest possible level of evidence [1].

Although the literature shows an increasing number of clinical trials, difficulties are still observed in surgical specialties to find a sufficient number of RCTs that can ensure a high level of evidence. This may imply that surgeons tend to be conservative regarding their own practices; only subtly modifying a procedure already performed apparently successfully [2,3,4,5].

Thus, under a more objective and analytical perspective, it is observed that there is a great deficit of evidence, that is, scientific demonstration, for many surgical and neurosurgical procedures. It is also observed in the literature that, too many authors, usual procedures and personal opinions end up working as scientific proof, which is knowingly not recommended within the scientific context [6]. Thus, quality of the neurosurgical clinical trials published is a cause of concern, as are the difficulties regarding adequate knowledge translation or the assessment of the scientificity of proposed treatments in neurosurgery [7,8,9,10,11,12].

To approach this topic, a survey to the surgeons members of the Brazilian Neurosurgery Society (BNS) was conducted to assess the transmission of scientific knowledge. Thus, the primary objective of this study was to assess the neurosurgeons' perception on the information sources and decision-making mechanisms regarding their medical practices. The secondary objectives were to characterize the importance given to several sources of knowledge, to identify the willingness of neurosurgeons to change their current practices and the factors involved in this decision, to characterize their perception of scientific trials and to identify differences in the transmission of neurosurgical knowledge among the different groups of neurosurgeons.

## MATERIALS AND METHODS

In September 2015, using a cross-sectional observational design, a questionnaire was sent to the 2400 members of the BNS. This questionnaire, specifically designed for this study and distributed through Survey Monkey™, contained 15 questions divided into 5 sections: characterization of the participants; perception of research in neurosurgery, decision-making process; the way knowledge is obtained and transmitted; how neurosurgeons handle new therapeutic alternatives; and analysis of ethical considerations in the conception and implementation of clinical trials. The BNS sent a link to the online survey to all its members, by email. Reminder emails were sent 3 times within 15 days. During these two weeks, a link and a request to fill out the questionnaire was also available on the BNS site (see the complete questionnaire as supplemental material).

The descriptive analysis of the response frequencies and the comparison between subgroups of time and place of practice was performed using confidence intervals in comparative analyses and the Pearson Chi-Squared test for the correlations. For cases with 20% or more of the observations with a response frequency lower than 5, the Fisher's Exact test was used. Statistical analyses were performed using SPSS 20.0™.

The responses were collected anonymously, jointly analyzed and only complete responses for each question were considered. The ethical committee of Lisbon Medical School and the Board of directors of the BNS were consulted for approval and saw no objections, deferred also the need for a formal informed consent.

## RESULTS

The response rate was 32% of the questionnaires sent, with 769 questionnaires filled out. From these, 87.5% (n=660) presented answers to all 15 questions and 22.5% (n=109) were partially answered.

More than half of the responders (53.3%) reported their professional activity duration as being over 10 years of practice. Among the professionals with less than 10 years of practice 15.6% were residents, 18.24% had less than 5 five years of practice and 12.7% between 5 and 10 years.

Over two thirds (67.8%) of the neurosurgeons performed activities in public hospitals, and 37.4% of them exclusively. From the total number of surgeons, 30.4% worked equally between public and private practices and only 13.2% exclusively performed private activities.

The participants' most frequent sub-specialties were spine (34.1%), followed by brain tumors, 29.3%. Other surgical subdivisions did not present high response rates: vascular 7.8%, pediatrics 5.6% and functional 3.3%.

**Source of information and research perception for the decision-making process**

In therapeutic decisions, neurosurgeons especially valued the education received during their specialty internship or residence (54.3%) and their personal professional experience (51.9%), whilst the consultation of information in the literature, protocols and academic experiences were reported by less than 30%. Concerning the information sources used weekly, 52.7% read scientific article abstracts; 46.8% checked the information available on the internet; 46.5% held rounds with colleagues and 45.0% consulted textbooks (Table 1).

| Response options | Daily | Weekly | Monthly | 1 or 2 times in the past year | None in the past year |
|---|---|---|---|---|---|
| Reading scientific article abstracts | 17.6% | 52.7% | 23.4% | 5.2% | 1.1% |
| Consultation of information available on the web | 34.1% | 46.7% | 15.5% | 2.7% | 0.9% |
| Discussions of therapies or management with neurosurgeon colleagues | 33.2% | 46.5% | 12.3% | 5.1% | 2.0% |
| Consulting textbooks | 19.1% | 44.9% | 27.1% | 7.7% | 1.1% |
| Participation in courses or workshop | 1.0% | 1.7% | 17.4% | 69.9% | 9.9% |
| Participation in national symposiums and congresses | 1.4% | 0.6% | 6.5% | 78.8% | 12.7% |
| Participation in international congresses | 1.0% | 0.3% | 1.7% | 44.5% | 52.5% |

Table 1. Frequency of consultation of sources of information

Lines by decreasing order for weekly responses, $p<0,005$

Regarding the perception of the interviewed neurosurgeons concerning their clinical practice, 87.9% believed that evidence-based medicine (EBM) is relevant or highly relevant and 93.3% also considered the surgeons' personal experience relevant or highly relevant (Table 2).

| Response options | Relevant | Very relevant | Little relevant | Irrelevant |
|---|---|---|---|---|
| Personal Experience | 51.0 % | 42,0% | 6.7% | 0.0% |
| EBM | 50.0% | 37.9% | 11.3% | 0.8% |

Table 2. Importance of the surgeons' professional experience and EBM in neurosurgery; EMB: Evidence Based Medicine; $p \leq 0{,}005$

Of all responders, 92.9% believed that the implementation of protocols for clinical decision making are relevant or highly relevant and 43.1% have protocols implemented in their neurosurgical services. Furthermore, 73.6% of the surgeons subscribed to some medical journal.

**Disposition to change the usual clinical practice**

The majority (82.6%) of the interviewees showed a personal willingness to modify their usual clinical practice if the goal was the improvement of the long-term outcomes (74.7%) and a reduction in severe complications (62.1%), with all other reasons below 40% of the responses. The participants that answered "not willing" to change their usual procedures, justified their answer for believing in the lack of scientific evidence to support the new procedure, and the learning curve for the use of a new technique with which they were not familiar, both with 48.2% of the responses obtained.

**Perception of clinical studies**

When requested to identify the most important types of scientific studies, they mainly valued cohort studies (63.2%), followed by case-controlled studies (52.8%), observational studies (49.1%) and clinical trials (43.1%). Responders used the following criteria to classify scientific articles as being excellent: levels and degrees of evidence (76.1%), strictness in the statistical analysis (56.1%), the existence of a control group (52.3%), and authors /institutions name in only 37.0% and 34.1% respectively, whilst the number of authors did not influence the attributed value of the article.

Regarding controlled studies, 65.5% perceived that the randomization improves the quality of controlled trials and 61.1% state being aware that these studies are not common in neurosurgery. The respondents report an intermediate level of familiarity with academic

concepts (Table 3), varying the percentage between 40.7% and 51.0% for all concepts presented (clinical guidance norms, guidelines, clinical cases, evidence-based medicine, therapeutic protocols, case series, evidence levels, systematic reviews, grades of recommendation, meta-analyses).

| Response options | Always or almost always | Most of the times | Somewhat frequently | Never or almost never |
|---|---|---|---|---|
| Education received during the specialty internship | 54.3% | 33.1% | 11.7% | 0.8% |
| Personal professional experience | 51.9% | 35.9% | 11.3% | 1.3% |
| Recent medical literature (less than one year) | 34.7% | 42.1% | 20.6% | 2.5% |
| Protocols or international guidelines | 34.0% | 35.8% | 24.2% | 6.3% |
| Medical visits | 30.4% | 28.5% | 26.6% | 14.5% |
| Protocols or guidelines/clinical guidance norms | 27.1% | 36.3% | 28.7% | 7.7% |
| Education received during the Medical course | 24.9% | 24.3% | 30.8% | 18.0% |
| Continued education (courses and congresses) | 24.0% | 33.7% | 37.4% | 4.8% |
| Protocols from the place they work | 23.6% | 31.1% | 26.6% | 18.7% |
| Opinions of neurosurgeon colleagues | 12.8% | 25.5% | 57.2% | 4.4% |

Table 3. Frequency of factors that influence the therapeutic decision making in neurosurgery Lines in decreasing order for the responses always or almost always; EBM:Evidence based medicine; $p \leq 0,05$ and CI 3,5-3,7

**Comparison between duration of practice**

When comparing groups by time in practice (≤10 vs. >10 years), those with up to 10 years of practice favor EBM, the learning received during internship and resorting to the recent literature and guidelines, whilst those with over 10 years of practice prefer personal opinions, case discussions with colleagues and attending more international congresses. There were no statistically differences in responses by practice location (public vs. private).

## DISCUSSION

Results from this cross-sectional survey indicate that Brazilian neurosurgeons especially valued the education received during the specialty internship and their personal professional experience, in detriment of consulting the literature data, protocols and others' academic experiences.

In their clinical practice, they valued EBM as well as the surgeons' personal experience, and showed a personal willingness to modify their usual clinical practice to improve their long-term outcomes and reduce complications. The more experienced the surgeons were, the more they relied on their practice and the less they relied on scientific literature [5,13].

They inadequately stratified and validated the different types of clinical studies, although they prefer scientific articles with high scientific evidence and refer that the randomization improves the quality of controlled studies.

When subdivided in function of clinical experience time, the younger ones prefer EBM and the more senior ones their personal experience. The 32% response rate was quite superior to other online medical questionnaires [14,15].

Professionals with more than 10 years of practice resort mostly to therapeutic conduct discussions with colleagues as learning resources in the last year, whilst the younger ones resort to the literature. These data corroborate the studies that point out not only that learning undergoes a historic evolution of its role and means of acquisition, but also that the development of competencies to search and use information to produce scientific knowledge may generate practical changes [16].

The individual professional experience and the opinion of neurosurgeon colleagues are considered priority in the neurosurgeon's day-to-day therapeutic decision making for the most experienced, whilst the younger ones prefer the education received during the internship, the recent literature, and guidelines [16]. In the neurosurgical sphere [17], there is a great emphasis and a tendency to prioritize the development of psychomotor faculties that guarantee the adequate surgical technique, leaving in the background the cognitive aspects, such as the investment in learning the scientific knowledge to back up the decision making within logical rationales. Nonetheless, an interest in scientific investment to back up the decision making and neurosurgical practice may be considered by some authors an ethical professional attitude [18].

The EBM concept was relevant to 87.9% of the respondents, whilst professional experience was important to 93.3% of them. This apparently irreconcilable dichotomy, when valuing

professional experience and EBM, is not foreign to other authors, that perceive that the construction of a surgeon, as the one that seeks better evidence for the decision making, is long and needs investments, requiring the search of researches databases and libraries with up-to-date material, as well as contact with centers of excellence and time spent with specialists to achieve the instruments of the evidence-based surgery practice [16,19,20].

Within this context, it is observed in the literature that there is a tendency to consider the professional with many years of experience in surgery as scientifically outdated and inclined to make decisions based on the empiricism and outcomes of their own practice [20,21].

The adoption of EBM includes the potential to improve professional qualification through the development of competencies, contribute to foster research and improve the use of diagnostic methods and the objectivity of the treatment. With that, better prognostic perspectives and life expectancy will probably appear, the costs in the treatment of patients might be reduced and the improvement in the quality of life will happen as a natural consequence of this process [5,17,19,22,23,24].

Although the introduction of clinical guidelines is positive in the sense of facilitating the review of the vast existing evidence, the great majority of the respondents consider them important, the actual transference of this importance for the organization by the implementation of the same is still below what is desired in a significant number of services [25,26].

The majority of the interviewees seem to present enough knowledge to orient themselves and seek relevant scientific studies. Nevertheless, they do not refer to familiarity with the classic concepts of study subtypes. Additionally, most surgeons did not have a clear idea of concepts such as the prevalence of controlled studies, the advantage of their random character and randomization itself, or about the scientific levels of neurosurgery publications. Thus, the relevance of enhancing scientific knowledge must be pointed out, especially directed to randomized controlled trials, due to their importance [27,28].

Some authors analyze the difficulties found in surgical clinical research standards and indicate many problems to perform randomized controlled trials in surgery: the structural, cultural and psychological resistance to the use of randomization, the variability inherent to surgery that requires a precise definition of the interventions, a strict monitoring of the quality, the surgery learning curves that poise difficulties to the time and execution of randomized trials for new techniques, the comparison of surgical and non-surgical treatments, and lastly, the rare, urgent

and life-threatening situations as causing difficulties in the recruitment, consent and randomization [2,3,6,11,27,29,30,31,32].

Furthermore, it must be pointed out that the inadequate stratification of research studies must serve as an alert for the need of greater clarification of their true knowledge on the different types of studies, considering that of the respondents mentioned subscribing to at least one scientific journal.

Within the concepts presented, making better choices regarding health and healthcare requires the best evidence possible, thus, as rich and different digital data sources become broadly available for research, and analytical tools continue to grow in power and sophistication.[2,3,18,30,33].

Research and health communities now have the opportunity to quickly and efficiently generate the scientific evidence necessary to support improved decision making in health and healthcare, without reducing the importance of specialists' opinions and qualitative information as a complementary source of knowledge. Thus, it is considered an opportunity to use qualitative methods to complement high-quality quantitative data within a more focused approach [2,3,18,30,33,34,35].

Therefore, surgical research must consider daily clinical surgery and surgical translational research issues, introducing new techniques and lab results in the assistance to the patient, and require clinical surgeons with competency in research. Consequently, it is necessary to allocate major efforts to the development and maintenance of high-quality surgical investigations in academic surgical departments, including individual career-advisory programs and clinical trial centers aiming at the attractiveness of academic positions in surgery, and the promotion of translational researches, as a benefit to patient care [12,36,37].

This study has limitations when analyzing answers of only a part of the set of neurosurgeons in the BNS, and the fact that those that answered might belong to subgroups of members that are more motivated or with greater familiarity with website platforms. However, the members of the BNS presented a questionnaire-response rate superior to other similar studies [14,15], can be divided into two similar groups with more or less than 10 years of neurosurgical experience, with most working in the public service, and mainly performing spine or brain-tumor surgeries. The concentration of responders in the early years of their career adequately reflects the age distribution of specialists in a country in which medical education in neurosurgery has increasingly progressed over the last 60 years [13]. The concentration in public hospitals reflects their association with treatment resources to treat patient with greater

complexity, whilst the preference for spine pathologies reflects the normal distribution [5,9,13,16,18] of neurosurgical subspecialties. Nonetheless it is not impossible that respondents may overestimate their use of resources, to unconsciously provide a positive view of themselves.

Although we included a large sample of the Brazilian neurosurgery, the extrapolation of the results must be considered with caution prior to the comparison of results with other national neurosurgeon samples or with other Brazilian surgeons.

## CONCLUSION

The members of the BNS that answered the questionnaire did so with an above-average response rate, with the majority working in public settings, especially performing spine or brain-tumor surgeries. Results differ by experience.

The most preferred information sources are weekly reading scientific-article abstracts, discussing conducts with colleagues and consulting textbooks. Here, the older surgeons prefer therapeutic discussions with colleagues and the younger ones consulting the literature.

The least experienced ones privilege the education received in their medical residence when doing therapeutic decision making, recent medical literature and national and international guidelines, whilst those more experienced prefer to rely on their individual professional experience.

When confronted with an innovative treatment alternative, they stated being willing to try it, especially taking into account the improvement of the outcomes and reduction of severe complications. When they did not consider changing their practice, they do so due to the lack of scientific evidence or the risks of using unfamiliar techniques.

The vast majority of the respondents attributed great relevance both to EBM and the surgeon's personal experience. They considered neurosurgical protocols as being very important, although less than half of them have protocols in place at their respective hospitals.

They also referred to having little familiarity with the interpretation of scientific concepts in the literature, despite identifying articles as being excellent due to their evidence level, highly-strict statistical analysis and the existence of a control group.

All this shows the need for implementing recommendations to improve the decision-making mechanisms. The BNS or other representing authority could eventually consider undertaking this responsibility.

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## *CHAPTER 4. IDENTIFYING RCTs IN NEUROSURGERY USING ELECTRONIC DATABASES*

**This section corresponds to the peer-reviewed manuscript with the reference:**

Gorayeb RP, Forjaz MJ, Ferreira AG, Duarte GNS, Machado T, Ferreira JJ. Electronic search strategies fail to identify randomized controlled trials (RCTs) in neurosurgery. 2019. Clin Neurol Neurosurg. 184:105446. doi: 10.1016/j.clineuro.2019.105446.


**ABSTRACT**

Randomized controlled trials (RCTs) are the gold standard studies to evaluate the efficacy of therapeutic interventions. Although they are frequently identified through open searches in electronic databases, no studies have evaluated how easy it is to identify RCTs in neurosurgery using electronic search strategies.

The present study evaluated the sensitivity and specificity of different search strategies applied to commonly used databases to identify RCTs in neurosurgery.

The total number of RCTs in neurosurgery published between 1960 and 2013 was determined through a detailed search involving open keyword searches in PubMed, Cochrane Library and Center for Reviews and Dissemination (CRD) databases, a PubMed search based on clinical entity-related keywords, and hand-searches on the reference list of identified articles. The sensitivity and specificity were calculated for the open keyword searches on PubMed, the Cochrane Library and the CRD database and for the Cochrane's HSSS, based on the total number of the identified RCTs.

Compared to the total of 1102 RCTs identified, PubMed open search yielded 4660 articles, among which 365 were RCTs (sensitivity: 33.1%; specificity: 7.8%). Cochrane open search yielded 621 among which 36 were RCTs (sensitivity: 3.2%; specificity:5.8%) and CRD open search returned 78 articles, among which 4 were RCTs (sensitivity: 0.4% sensitivity; specificity: 5.1%). The Cochrane HSSS retrieved 10702 results, among which 340 were RCTs (sensitivity: 30.9%; specificity: 3.2%).

Most RCTs in neurosurgery cannot be identified by commonly used search strategies, which emphasizes the need to improve their indexing.

## INTRODUCTION

In medical research, Randomized Controlled Trials (RCTs) are the gold standard clinical studies to assess the efficacy of therapeutic interventions [3]. It is therefore crucial that RCTs are easily identified by health professionals and other decision-makers, thus allowing access to the best available information.

Neurosurgery is no exception, and the concept of 'evidence-based neurosurgery' (EBN) has recently been proposed [9], according to which the patient care framework is built upon integrating clinical/surgical expertise, patient's preferences and values, clinical circumstances and the best available research evidence.

The International Committee of Medical Journal Editors (ICMJE) recommends the standardization of medical data published in indexed journals. While, on one hand, this provides an opportunity to enhance data sharing, on the other hand, high profile trials and those that are particularly easy to find will be cited and used more often, which may lead to biased healthcare decisions [28]. Broad and well-implemented search strategies are therefore essential to identify as many relevant studies as possible, avoiding biased reviews and laying the foundation for sound decision-making [10,20].
Electronic search strategies aim to facilitate the identification of studies on specific topics of interest [13]. To be effective, such strategies must be able to identify as many relevant studies as possible (i.e., be sensitive), while excluding as many irrelevant studies as possible (i.e., be specific) [12].

Most search strategies rely on electronic databases, with the PubMed and Cochrane library being the most commonly used [14,15,17]. To maximize the sensitivity and specificity of electronic searches, a comprehensive search strategy—the Cochrane High Sensitivity Search Strategy (HSSS)—was developed and published in 1994 and adapted over time [8]. It remains widely used and is still considered as the best available search strategy; thus it is frequently cited in comparative studies of search methods [16].

To date, no studies have investigated how easy it is to identify RCTs in neurosurgery in commonly used databases.

The sensitivity and specificity of different search strategies to identify RCTs in neurosurgery were evaluated.

## METHODS

RCTs in neurosurgery, defined as randomized trials with two or more comparative groups, and at least one neurosurgical therapeutic intervention, were included.
Search results were identified as RCTs in neurosurgery by one author (RG), through the information available in title, abstract or full text. A second author (JJF) was consulted for cases in which eligibility was unclear.

The total number of RCTs in neurosurgery published between 1960 and December 31, 2013 was determined through a detailed search, which included the following steps: a) open electronic searches on PubMed, the Cochrane Library, and the Centre for Reviews and Dissemination (CRD) databases, using "RCTs" and "neurosurgery" as keywords; b) a PubMed search using keywords related to neurosurgical clinical entities (i.e., publication type = 'randomized controlled trial' AND (pathology subtype) AND date-publication='1960/01/01':date-publication=2013/12/31), and c) hand-searches on the reference lists of the identified RCTs, systematic reviews and meta-analyses (Figure 1).
Duplications and abstracts were excluded from the total number of retrieved results, leading to the final list of published RCTs.

Once the final list was obtained, the search strategies most frequently applied to biomedical databases were assessed regarding the number of RCTs retrieved. These included the keyword searches applied to PubMed, the Cochrane library and the CRD databases, and the Cochrane's High Sensitivity Search Strategy applied to PubMed. Based on the findings of this assessment, the specificity and sensitivity of each of those search strategies were determined.

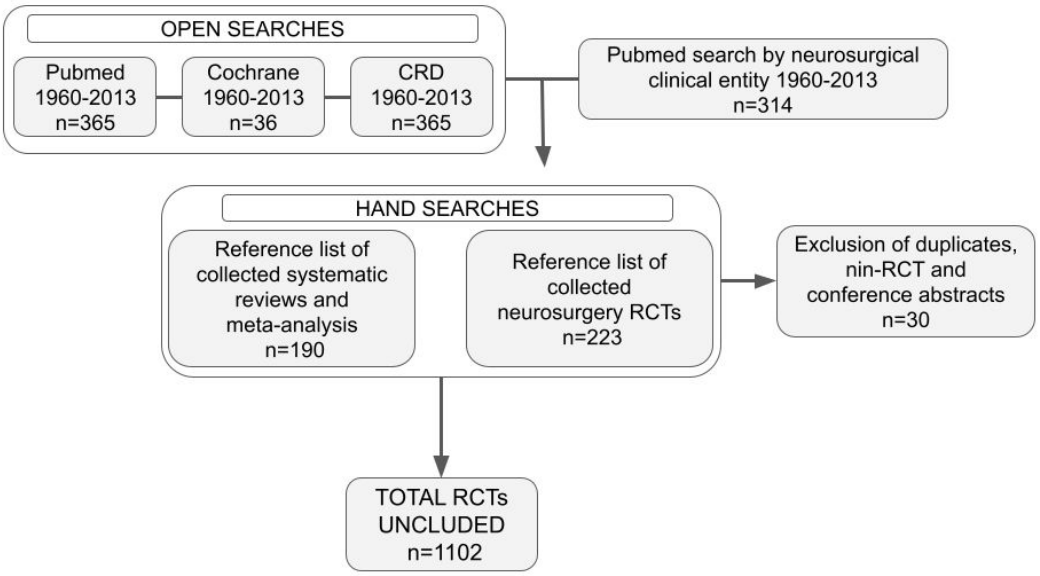


Figure 1. Detailed search strategy performed on electronic databases and reference lists to identify the final list of RCTs in neurosurgery published between 1960 and 2013. The oldest RCTs identified were published in 1960.

*Data Analysis*

Unless stated otherwise, results are presented as sums, percentage and means.

Sensitivity (i.e., the ability to identify as many RCTs as possible) was calculated as follows: number of RCTs identified by each specific search strategy / total number of RCTs identified. Specificity (i.e., the ability to exclude as many irrelevant results as possible) was calculated as follows: number of RCTs identified by each specific search strategy / total number of articles returned by that particular search strategy.

**RESULTS**

A total of 1102 RCTs in neurosurgery were identified. The number of RCTs identified by each step of the detailed search is presented in Table 1. Open searches using "RCT" and "neurosurgery" as keywords (a) identified a total of 405 RCTs in neurosurgery, among which 365 were identified in PubMed, 36 in the Cochrane library and 4 in the CRD database. Among these, 30 were excluded as duplicates or abstracts, leaving a total of 375 RCTs to be used for further analyses. The PubMed search using clinical entity-related keywords (b)

identified 314 RCTs, whereas hand-searching the references of previously identified RCTs, and systematic reviews and meta-analyses (c) retrieved 223 and 190 RCTs, respectively.

| Phase | Search strategy | Number of results |
|---|---|---|
| a) | Open Search on PubMed, Cochrane and CRD, using 'RCT' AND 'Neurosurgery' as keywords | 375 |
| b) | RCT AND Pathology Subtypes | 314 |
| c) | References of previously identified systematic reviews and meta analysis | 190 |
| | References of previously identified neurosurgery RCT | 223 |
| Total | | 1102 |
| e) | Cochrane's High Sensitivity Search Strategy (HSSS) | 340 |

Table 1 – Number of RCTs in neurosurgery identified by each search for the 1960-2013 period. RCT- Randomized Controlled Trial; CRD – Centre for Reviews and Dissemination; SR – Systematic Reviews; MA – Meta-analysis

Results concerning the sensitivity and specificity of each search strategy are presented in Table 2.

Open searches on PubMed using "RCTs" and "neurosurgery" as keywords retrieved 4660 results, among which 365 were identified as RCTs. This granted PubMed with a sensitivity of 33.1% and a specificity of 7.8%. When the same keywords were used to search the Cochrane library, 621 articles were retrieved, among which 36 were classified as RCTs. This granted the Cochrane library with a sensitivity of 3.2% and a specificity of 5.8%. Using the same keywords to search the CRD database retrieved 78 articles, among which 4 were identified as RCTs. This granted the CRD with a sensitivity of 0.4% and a specificity of 5.4%.

The Cochrane HSSS applied to PubMed retrieved 10702 results, among which 340 were RCTs in a neurosurgical indication, granting the HSSS with a sensitivity of 30.9% and a specificity of 3.2%.

| | Articles returned | Nº RCTs | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| PubMed | 4660 | 365 | 33.1 | 7.8 |
| Cochrane | 621 | 36 | 3.2 | 5.8 |
| CRD | 78 | 4 | 0.4 | 5.1 |
| HSSS in PubMed | 10702 | 340 | 30.9 | 3.2 |
| Total RCT = 1102 | | | | |

Table 2 – Comparison among open searches on PubMed, Cochrane Library and CRD and Cochrane's HSSS, in terms of sensitivity and specificity to identify RCTs in neurosurgery. RCTs- Randomized Controlled Trials; CRD – Centre for Reviews and Dissemination; HSSS – High sensitivity search strategy.

## DISCUSSION

The present study evaluated the sensitivity and specificity of different search strategies to identify RCTs in neurosurgery. We found that most published RCTs in neurosurgical indications cannot be identified through commonly used electronic search strategies. From the total of 1102 RCTs published in English until the end of 2013, open keyword searches identified 33% in PubMed, 3% in the Cochrane library and less than 1% in the CRD database. Surprisingly, the Cochrane HSSS applied to PubMed did not present a higher sensitivity or specificity than open searches, identifying only about 31% of the total number of published RCTs. Several studies in other fields of medical research have previously addressed the sensitivity and specificity of the HSSS applied to PubMed. Marson and Chadwick [21] used different search strategies applied to PubMed to identify RCTs in epilepsy and found that a basic search had a sensitivity and specificity of 66% and 35%, respectively, whereas a comprehensive search had a sensitivity of 86% and a specificity of 72%. Chow et al. [4] compared Cochrane's optimal search strategy with a standard PubMed search and with their own algorithm to search PubMed and EMBASE, to identify RCTs in pain research. They found that the sensitivity of each method was 99.6%, 65% and 97% respectively, whereas the specificity was 78%, 97% and 98%, respectively. Sjögren and Halling [25] performed PubMed searches to identify RCTs in dental research and found that the sensitivity and specificity of each search varied widely among different areas of dental research, with the

sensitivity ranging between 5% (pediatric dentistry) and 100% (orthodontics), and the specificity ranging between 81% (public health dentistry), and 100% (pediatric dentistry and oral surgery). While the reported values of sensitivity and specificity varied widely across medical fields, one finding common to all studies is that the number of RCTs identified was strongly limited by inadequate indexing and methodological reporting, especially in the abstract. This is consistent with the findings of the present study, where several studies failed to be retrieved by the investigated search strategies due to inadequate indexing. Examples include the RCTs by Kraemer et al. [19] and Smorgick et al. [26], which were not retrieved through open searches on PubMed and lacked relevant keywords in the title although the manuscript text contained enough information about the trial design. Similarly, a trial by Schuurman et al [24], which was not retrieved by the Cochrane's HSSS, contained a good description of the study design on the Methods section, but lacked relevant keywords in the title and abstract. Similar cases were found for the searches on the Cochrane Library and CRD database.

The need to improve the reporting of RCTs in neurosurgery was previously identified by a review of RCTs published between 2006 and 2007 [18]. The authors of that study looked at RCTs published in reference neurosurgery and medical journals and found that among the neurosurgery journals the quality of reporting was much poorer than in the medical journals (mean JADAD score: 2.45 vs 3.42, for neurosurgery and medical journals, respectively; CONSORT score: 26.5 vs 41, respectively). Further studies, looking at wider time frames could therefore be useful to investigate how this issue has changed over time.

In the present study, the total number of RCTs in neurosurgery identified for the target period could only be determined by combining different searches in several databases. This shows that, within this research field, no single electronic search strategy can identify all published RCTs. This finding is not surprising, as a previous review has reported that thorough multiple-source searches are required to maximize the number of results [7].

The present study included only searches performed in generalist biomedical online databases, with no searches performed on clinical trial registries, such as the clinical trials.gov or EUDRACT.

While clinical trials registries may constitute the easiest way to identify RCTs and have been considered an important tool when performing systematic reviews [14], they include all registered trials, irrespective of the performance stage, which may not be the most effective way to gather the best information to support health-care decisions.

A previous systematic review of search strategies to identify RCTs of chronic depression [29] reported that 84% of the identified studies were gathered through electronic database searches whereas 16% were gathered through additional searches, including clinical trial registries (ClinicalTrial.gov and ICTRP). From those 16%, hand-searching the reference lists of systematic reviews had the highest contribution (10%), whereas searching clinical trial registries had the lowest contribution (0%). On the other hand, Baudard et al. [1] reviewed all systematic reviews of pharmaceutical treatments published between 2014 and 2015 and reported that about half of the analyzed reviews did not search clinical trial registries. Upon searching clinical trial registries, the authors identified additional studies for 43% of those reviews. However, reanalysis of 14 meta-analysis with inclusion of the additional articles revealed no quantitative or interpretative changes of the results.

While previous studies suggest a low impact of searching clinical trial registries, further research is needed to evaluate the contribution of clinical trial registries to identify RCTs in neurosurgery.

Among the used databases, PubMed searches had higher sensitivity and specificity than those performed on the Cochrane library and the CRD, which may be related with the number of articles indexed in each of those databases.

Several previous studies have reported that the sensitivity of simple- and optimized-search strategies ranges between 2-51% and 67-99%, respectively [11,16, 23]. Our results are consistent with such finding, as the total number of identified RCTs could only be achieved by combining several searches.

The Cochrane HSSS is still considered to be the best electronic search tool and to maximize sensitivity and specificity [14,16]. However, our results suggest that, in the field of neurosurgery, this search strategy is not effective. This may be partly due to the lack of specificity regarding the surgical techniques, reflecting inadequate indexing and methodological reporting in RCTs in neurosurgery. In fact, most developed search filters rely on the reported methodological information [22], especially that included in the abstract. This result raises concern regarding the methodological reporting of RCTs in neurosurgery, highlighting a need for review studies to critically appraise them.

Finally, the present study focused on RCTs. While RCTs remain the gold standard studies to evaluate the efficacy of new interventions, in neurosurgery their performance is limited by several specific challenges related to patient recruitment, inclusion of an appropriate control group, surgical selection bias, lack of equipoise, among others [6]. Although prospective,

observational studies have often been considered to overestimate therapeutic effects for being subject to external confounds [27], recent studies have found no significant differences between the results of RCTs and cohort or case-control studies [2, 5].

Therefore, prospective observational studies may constitute an important source of information supporting the use of new surgical techniques, and further studies would be useful to evaluate their impact in the development of new neurosurgical interventions as well as their accessibility through commonly used electronic search strategies.

## CONCLUSION

In conclusion, easy access to all published RCTs is crucial for systematic reviewers, meta-analysts and especially health care decision-makers. RCTs in neurosurgery are not easily identified using common search strategies, thus trial indexing should be improved, and the reporting of methodology should be evaluated.

Failure from commonly used search strategies to identify most RCTs should be a source of concern for researchers in all fields of medicine.

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Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with financial interest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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## *CHAPTER 5. THE SCIENTIFIC QUALITY OF RCTs IN NEUROSURGERY*

**This section corresponds to the submitted manuscript:**

Gorayeb RP, Forjaz MJ, Ferreira AG, Ferreira JJ. Low quality of randomized controlled trials in neurosurgery: results from a critical appraisal of 1102 RCTs


### ABSTRACT

**Background:** Randomized controlled trials (RCTs) are the best studies to evaluate the efficacy of therapeutic interventions. The quality of RCTs in neurosurgery is not clear and needs to be evaluated.

**Objective:** To critically appraise the design and reporting quality of RCTs in neurosurgery.

**Methods:** Randomized trials with two or more comparative groups and at least one neurosurgical intervention were identified in commonly used databases. Study design and other methodological aspects were analyzed. The quality of included RCTs was assessed using the Cochrane Risk of Bias tool.

**Results:** A total of 1102s RCTs in neurosurgery were identified. The number of published RCTs increased steadily from 1980, with most being published after 2000 (mean=70.5 articles per year). Most RCTs focused on surgical interventions of the spine (47.9%), cranium (21.2%) and peripheral nerves (6.4%), whereas 18.1% focused on pain management and 6.4% on the treatment of movement disorders and other clinical problems. Most RCTs lacked information on study design (93.6%), randomization method (59.9%), blinding (59.8%), and data analysis (76.3%). Although the overall risk of bias decreased over time, 25.5% of the RCTs published between 2010 and 2013 lacked a clear risk of bias classification due to insufficient critical information. The methodological aspects more frequently classified with high risk of bias were “blinding of participants and personnel” (21.2%) and “incomplete outcome information” (28.8%).

**Conclusion:** Although the quality of RCTs in neurosurgery has improved to some extent, several methodological aspects need further urgent improvement to minimizing bias and ensuring a correct data interpretation.



**Keywords:** Neurosurgery; randomized controlled trial; RCTs; risk of bias; appraisal; methodology.

## INTRODUCTION

Randomized controlled trials (RCTs) are the gold standard studies to investigate the causal relationships between treatment and outcome.[1] Nonetheless, evidence shows that their quality is suboptimal, especially in the case of RCTs in surgery,[2] which may be due to the lack of methodological rigor and failure to report critical information.[3-8] It has previously been reported that RCTs in cancer and surgery often reflect the lack or inadequate use of randomization and blinding (especially outcome blinding) and fail to report information such as inclusion criteria and follow-up schedules.[9,10]

Trial validity, results interpretation and technique replication strongly rely on an adequate methodology and transparent reporting.[11] Therefore, several checklists have been created to improve the quality and reporting of RCTs. One such example is the CONSORT Statement,[12] which includes an extension addressing non-pharmacological interventions, such as surgery.[13]

Improving the methodology of trial design and reporting is therefore crucial,[14] and the single factor determining trial quality is minimizing bias.[15] In fact, it has been suggested that a trial's internal validity may be compromised by the risk of bias.[16,17]

It has previously been reported that the quality of RCTs in surgery (including neurosurgery) is low and limited by specific difficulties inherent to the field.[2] However, in neurosurgery this remains controversial, with some authors acknowledging these limitations,[18] while others consider that the quality of RCTs in neurosurgery is satisfying and continues to improve.[19,20] It is, therefore, necessary to systematically evaluate the quality of published RCTs in neurosurgery.

The present study critically appraised published RCTs in neurosurgery, in terms of reported design and other methodological information and risk of bias.

## MATERIALS AND METHODS

### Study design

A systematic review of the study design and methodological characteristics of RCTs in neurosurgical indications.

**Sample collection**

RCTs in neurosurgery, defined as randomized trials with two or more comparative groups and at least one neurosurgical therapeutic intervention, published before December 31 of 2013, were identified through open keyword searches on PubMed, the Cochrane library and the Centre for Reviews and Dissemination (CRD) database, a PubMed search using clinical entity-related keywords and hand-searches on the reference lists of the identified RCTs, systematic reviews and meta-analysis.

Studies were identified by the authors, based on the information provided by the title, abstract and methods. Duplicates, abstracts and non-RCT studies were excluded.

The search strategy flowchart is presented in Figure 1.

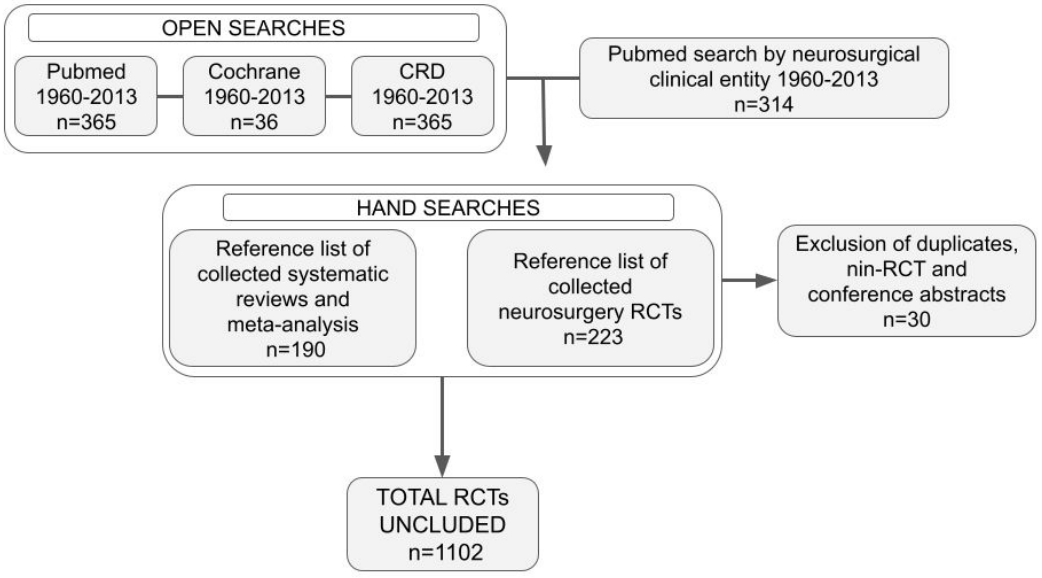


Figure 1. Flowchart with the electronic and hand search strategy used in this study. The first published RCTs in neurosurgery were from 1960.

**Data extraction**

Extracted information was entered into a data collection form and included the following methodological aspects: type of study design, inclusion criteria, study outcomes, sample size and its calculation method, dropouts and loss to follow-up, methods of randomization and blinding, statistical analyses, type of control, follow-up duration, reference to adverse events and description of interventions. All aspects were classified as either reported or not reported. In addition, the type of study design, type of outcome, sample size, dropouts and loss to

follow-up, methods of randomization and blinding, type of statistical analyses, type of control and duration of follow-up were also registered.

The information was extracted by one author (RG), and a second author (JJF) was consulted in cases of unclear information, or when there was any doubt regarding how to clarify the information.

Each RCT was classified according to the Cochrane risk of bias tool, as previously described.[21] The following methodological aspects were classified with either as "High", "Low" or "Unclear" risk of bias: selection bias (i.e., random sequence generation and allocation concealment); performance bias (i.e., blinding of participants and personnel); detection bias (i.e., blinding of outcome assessment); attrition bias (i.e., occurrence of incomplete outcome data); reporting bias (i.e., selective outcome reporting); and other bias (i.e., other sources of bias, such as industry sponsorship). Subsequently, an overall risk of bias was determined for each RCT, which corresponded to the most prevalent classification. Trials with an equal number of methodological aspects classified with "High" and "Low" risk of bias, received an overall classification of "Medium" risk of bias.

The publication dates were analyzed to investigate the changes in the number of RCTs published per year, and the studies were divided into six decades, to investigate changes on the risk of bias over time (1960-1969, 1970-1979, 1980-1989, 1990-1999, 2000-2009, 2010-2013).

**Statistical analysis**

Data analyses were performed using the SPSS software (v22.0 - IBM). Unless stated otherwise, results are presented as numbers and percentages. The Spearman correlation was used to analyze the association between the reporting of critical information and the publication date, thus evaluating how reporting evolved over time. A level of $P < 0.05$ was considered statistically significant.

## RESULTS

A total of 1132 articles were identified: 405 through open keyword searches, 314 through clinical entity-related keyword searches and 413 through hand-searching of reference lists (Figure 1). After the exclusion of non-RCTs, duplicates and abstracts, a total of 1102 RCTs in neurosurgery were used for analysis.

*Number of trials published per year*

The distribution of the 1102 RCTs over time is presented in Figure 2. The number of publications increased steadily between 1980 and 2013, with a yearly publication of £ 0.6% until 1989 (average=2.5; range:1-7 publications per year), 0.8%-2% from 1990 to 1999 (average=14.6; range: 9-25 publications per year), 3-5% from 2000 to 2004 (average=41.3; range:36-52 publications per year), 4-8% between 2004-2012 (average=70.1; range: 48-87 publications per year) and 9% in 2013 (n=100).

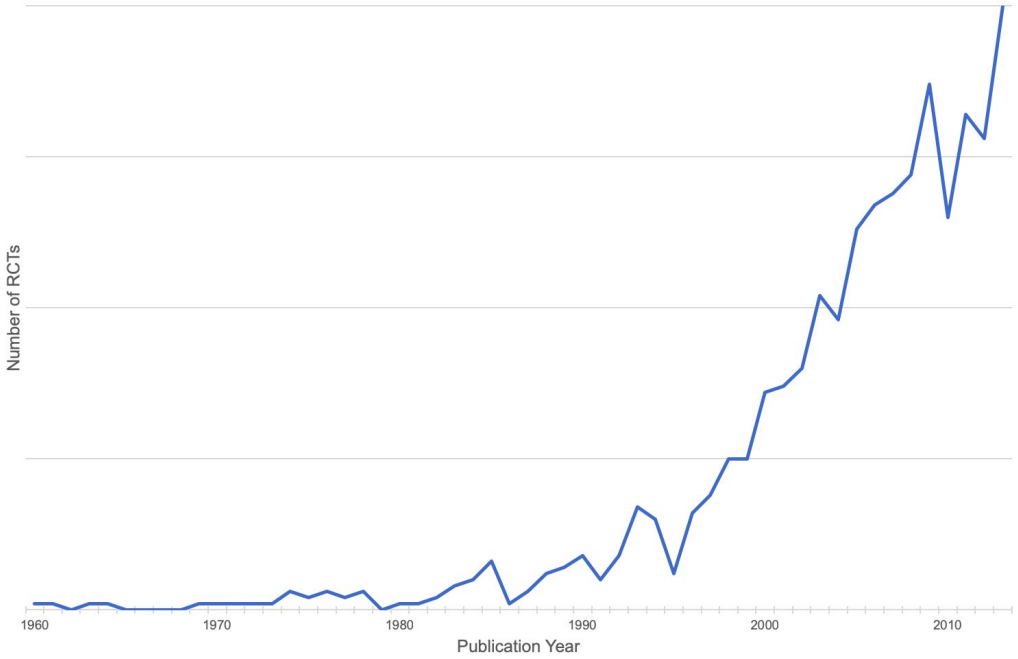


Figure 2. Number of RCTs identified per year of publication

*Target interventions, anatomical areas and diseases*

Information concerning the target interventions, anatomical areas and diseases is presented in Table 1. Most included RCTs (75.5%) concerned surgical interventions of the spine (47.9%), cranium (21.2%) and peripheral nerves (i.e., carpal tunnel, cubital nerve and brachial plexus) (6.4%). A total of 200 RCTs (18.1%) focused on methods to treat pain, and 70 (6.4%) studied

treatments for movement disorders and other clinical problems such as Parkinson's disease, Tourette's syndrome and epilepsy.

| Intervention | n | % |
|---|---|---|
| Cranial surgery | 234 | 21,2 |
| Spine surgery | 528 | 47,9 |
| Peripheral nerve surgery | 70 | 6,4 |
| Treatment of pain (detailed bellow) | 200 | 18,1 |
| Intradiscal injections and IDET | 28 | 2,5 |
| Spine infiltrations | 129 | 11,7 |
| Other infiltrations (non spine) | 19 | 1,7 |
| Facet radiofrequency (thermal/pulsed) | 24 | 2,2 |
| Treatment of movement disorders and other clinical problems | 70 | 6,4 |

Table 1. Number and percentage of identified RCTs (n=1102) according to the target interventions

*Study design*

Most RCTs failed to report critical methodological information. A total of 1039 RCTs (94.3%) lacked information on study design, 841 (76.3%) did not report the type of statistical analyses performed (i.e., intent-to-treat vs per protocol), 777 (70.5%) did not report sample size calculation, 660 (59.9%) did not report the method of randomization and 659 (59.8%) did not report the type of blinding.

Moreover, 707 RCTs (64.2%) did not distinguish between the primary and secondary outcomes, whereas 4.9% did not report the measured outcomes.

Information on inclusion criteria was lacking in 102 (9.3%) RCTs.

*Reported methodological information*

Information on methods

The authors did not assume any type of design based on the information gathered from the overall reading of the text, other then that explicitly reported. Among the 70 RCTs that contained information on the trial design, most reported either a parallel (n=39; 3.5%) or a cross-over design (n=22; 2%). The types of experimental design reported are presented in Table 2.

| Reported study design | n | % |
|---|---|---|
| Parallel | 39 | 3,5 |
| Cross-over | 22 | 2,0 |
| Factorial | 2 | 0,2 |
| Not reported | 1039 | 94,3 |

Table 2. Number and percentage of identified RCTs (n=1102) according to the reported study design

Among the RCTs containing information on randomization and blinding, the most commonly reported randomization methods were computer-generated allocation (n=230; 20.9%) and pre-sealed envelopes (n=136; 12.3%), whereas the most commonly reported type of blinding was double-blinding (n=299; 27.1%) (Table 3, Figure 3).

| Reported methods of randomization | n | % |
|---|---|---|
| Computer-generated allocation | 230 | 20,9 |
| Pre-sealed envelopes | 136 | 12,3 |
| Independent randomization center | 36 | 3,3 |
| Registration number | 15 | 1,3 |
| Card draw | 13 | 1,2 |
| Coin toss | 12 | 1,1 |
| Not reported | 442 | 40,1 |

Table 3. Number and percentage of identified RCTs (n=70) according to the reported randomization method

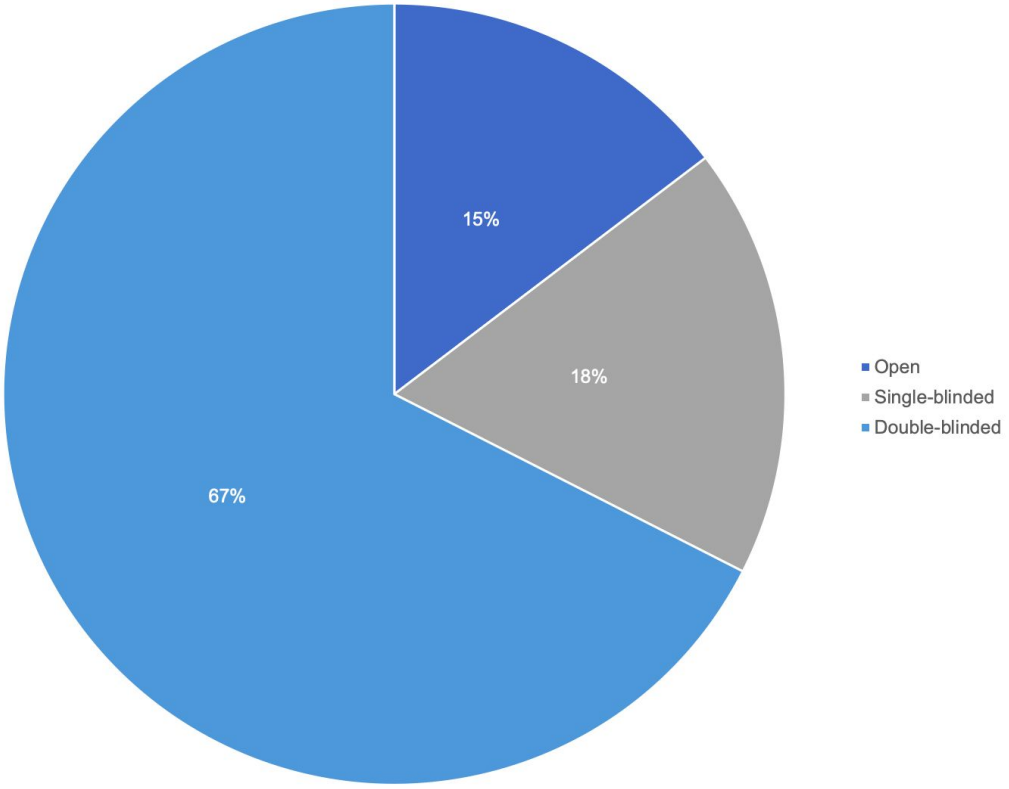


Figure 3. Type of blinding reported in the identified RCTs in neurosurgical indications (n=70)

Information pertaining to the type of control used is presented in Table 4. Most analyzed RCTs used non-pharmacological interventions as control (N=816; 74%), whereas 140 (12.7%) used pharmacological interventions and 81 (7.4%) used sham interventions.

Among RCTs using sham intervention, most (43.2%) involved injections to administer a placebo solution either into the spine (32.1%) or peripheral nerves (11.1%). Cranial surgery was performed in 22 RTCs (27.2%), among which 12 (14.8%) used cranial implant surgery for sham deep brain stimulation, 7 (8.6%) concerned the intraoperative administration of a placebo solution and 3 (3.7%) used sham surgery comprising scalp incision and partial burr holes without dura mater penetration. Spine surgery was performed in 12 RCTs (14.8%), among which 10 consisted of the intraoperative administration of a placebo solution, and two consisted of pre- and post-operative administration of a placebo solution. Insertion of probes or catheters for sham lesion was performed in 12 RCTs (14.8%), among which 10 used radiofrequency, 2 used IDET and 1 used percutaneous epidural lysis.

A total of 65 (5.9% RCTs did not use a control, simply following up the patients without any treatment.

| Reported control | n | % |
|---|---|---|
| Non-pharmacological interventions | 816 | 74,0 |
| Pharmacological interventions | 140 | 12,7 |
| Sham interventions | 81 | 7,4 |
| Patient follow-up (no other control) | 65 | 5,9 |

Table 4. Number and percentage of identified RCTs (n=1102) according to the type of control used

The most commonly reported outcome measures were symptomatic (n=1041; 94.5%), with only 61 RCTs (5.5%) reporting survival/mortality outcomes.

An "intent-to-treat" analysis was used by 211 (19.15%) RCTs, whereas 50 (4.5%) analyzed data "per protocol".

Information on participants and follow-up. Information regarding sample size, dropouts and loss to follow-up is presented in Figures 4 and 5.

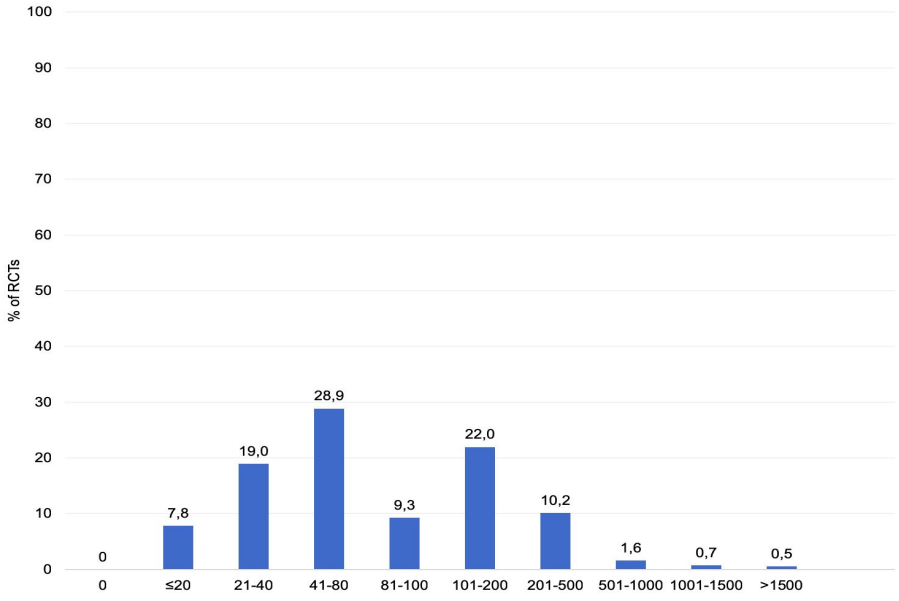


Figure 4. Percentage of the identified RCTs (n=1102) according to the sample size

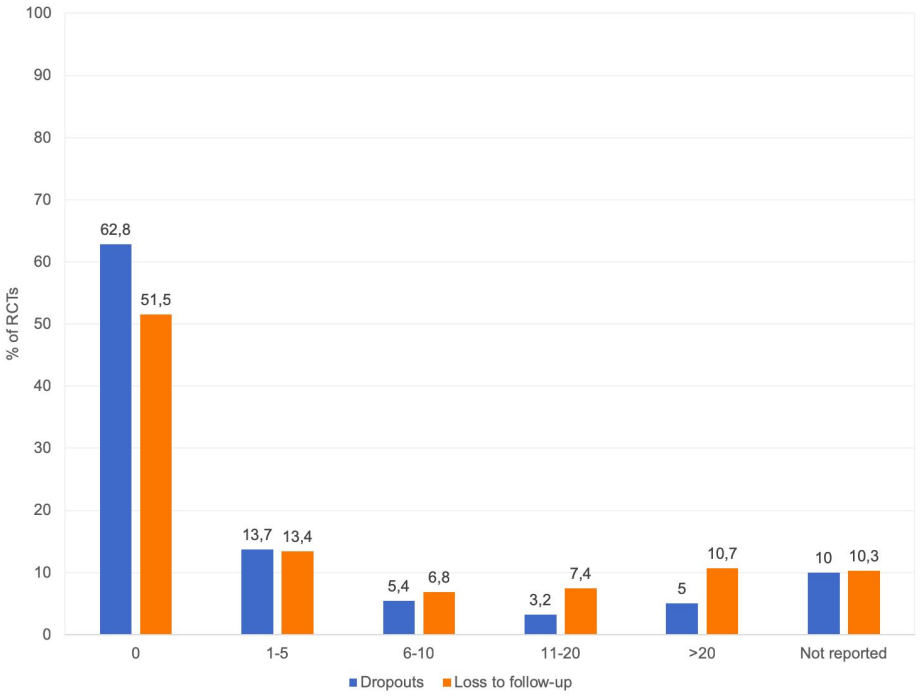


Figure 5. Percentage of the identified RCTs (n=1102) according to the number of dropouts and participants lost to follow-up.

Most RCTs included less than 100 participants (n=715; 64.8%), with the highest proportion including 41 to 80 participants (n=318; 28.9%). Among the 1102 RCTs, 692 (62.8%) reported not to have any dropouts, whereas 110 (10%) failed to report that information. Among the RCTs with dropouts, the highest proportion had 1-5 dropouts (n=151; 13.7%). Regarding the loss of patients to follow-up, 567 (51.7%) RCTs did not lose any patients to follow-up, whereas 113 (10.3%) failed to report that information. Among the RCTs that lost patients to follow-up, most lost between 1-5 patients (n=148; 13.4%).

The average follow-up duration was 19.6 months, and it ranged between 12h and 27 years. The most commonly reported follow-up duration was 6 months or less (n=379; 34.4%) (Figure 6).

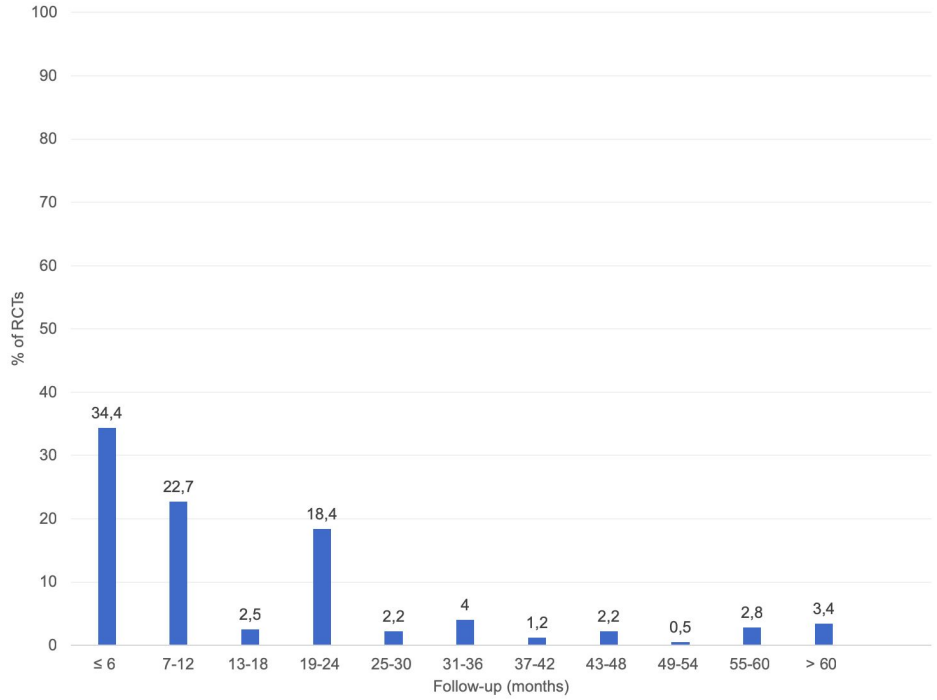


Figure 6. Percentage of identified RCTs (n=1102) according to follow-up duration (months)

*Evolution over time*

Spearman correlation revealed a significant, positive relationship between the date of publication and the reporting of both the method of randomization ($r=0.194$; $p<0.01$) and the type of blinding ($r=0.187$; $p<0.01$), indicating an improvement of these two methodological aspects over time.

*Risk of bias*

The risk of bias classification for the analyzed RCTs is presented in Figure 7. The two methodological aspects most frequently classified with "High" risk of bias were "Incomplete outcome data" (n=319; 28.9%), and "Blinding of patients and personnel" (n=235; 21.3%). Conversely, the methodological aspect most frequently classified with "Low" risk of bias was "Selective outcome reporting" (n=806; 73.1%), whereas the item most frequently classified as "Unclear" was "Allocation concealment" (n=753; 68.3%).

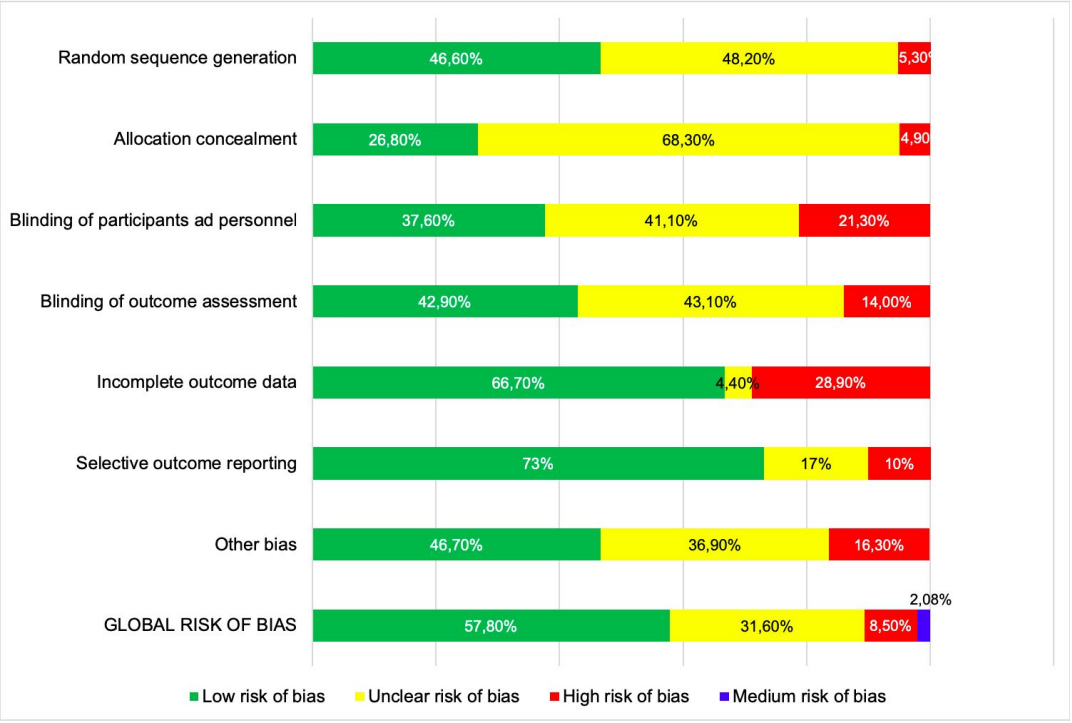


Figure 7. Evaluation of the Risk of Bias, using the Cochrane Risk of Bias Tool. The global risk of bias was determined based on the number of High, Low and Unclear classifications of each risk of bias aspect.

Determining the overall risk of bias for each analyzed decade (Figure 8), showed that the number of studies classified as "Unclear" decreased steadily over time, whereas those classified as "Low" increased over time. Although the number of studies classified with "High" and "Medium" risks of bias did not follow a steady tendency, since the 80s they remained under 10% and 3% respectively.

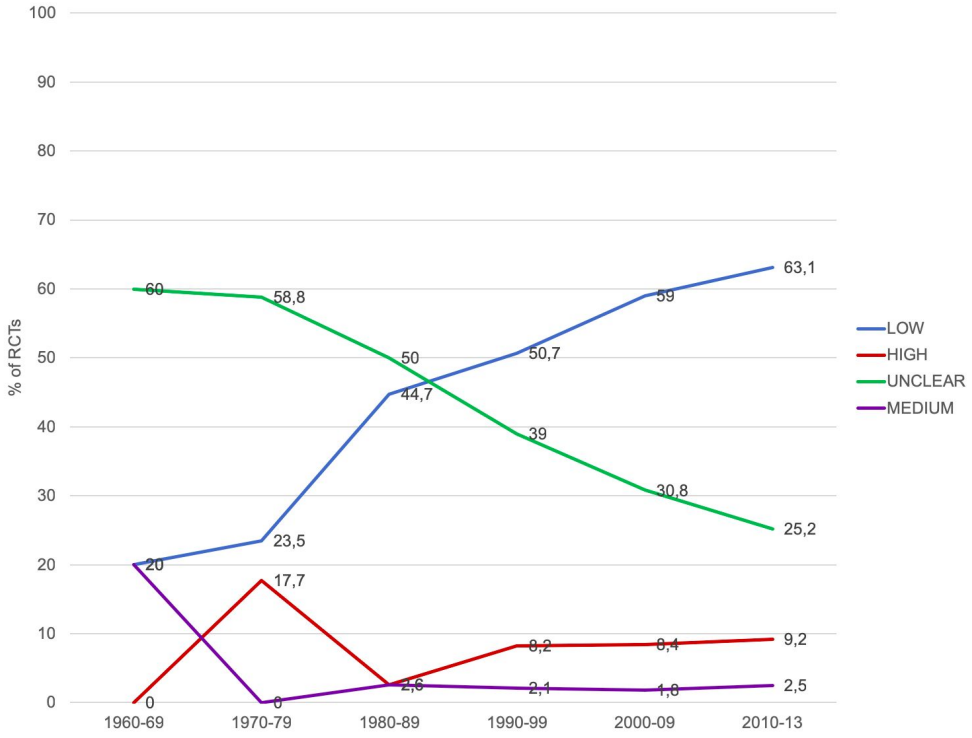


Figure 8. Percentage of the identified RCTs (n=1102) classified with an overall risk of bias of High, Low, Medium and Unclear, per publication decade.

## DISCUSSION

The present study provides a critical evaluation of the design, methodology and reported quality of all RCTs in neurosurgery published between 1960 and 2013.

The number of RCTs published per year remained constant until the end of the 1970s, after which it increased steadily until the end of 2013. This result reflects a tendency similar to that previously reported by Kiehna et al.[3] of a growing number of RCTs published in this field.

Most RCTs lacked critical information such as the type of study design, method of randomization, information on blinding, and type of statistical analyses performed.

It has previously been discussed that different types of design, such as parallel and cross-over, affect the trial's statistical power and influence the results obtained.[22,23] Therefore, adequate results' interpretation and trial's replicability rely on the reporting of the study's design characteristics. The fact that over 90% of the RCTs included in our review failed to report this

information, highlights an urgent need to improve the methodological reporting of RCTs in neurosurgery.

Randomization avoids selection and allocation biases by addressing potential confounding variables.[24,25] It is therefore crucial for a rigorous design of controlled trials. Several previous reviews, performed in different time-periods and in various fields of medical research, have pointed out the lack of information regarding the randomization method.[26-28] RCTs in neurosurgery are one such example.[27] In the present study, although all analyzed RCTs indicated that randomization was performed, about 60% lacked information on the randomization method, thus preventing an adequate evaluation of the allocation concealment.

Similarly, blinding—which was reported in only 40% of the RCTs analyzed—is crucial to ensure the robustness of clinical trials by avoiding several sources of bias[29]. A previous review of RCTs in traumatic brain injury[30], reported that among those published between 2002 and 2010, 56,9% included the type of blinding, whereas among those published between 2011 and 2013 only 31,3% provided that information. Similarly, two reviews performed by Mansouri et al.,[31,18] in neuro-oncology and neurosurgery, revealed that blinding was one of the most poorly reported methodological aspects. These results, which are consistent with the findings of the present study, indicate that the report of blinding is suboptimal and has not improved significantly over time.

Analysis of the sample size showed that most trials included a sample of less than 100 patients, with the highest proportion including 41-80 patients. An adequate sample size is required to ensure a high power of the experiments, hence avoiding type I and II errors. However, our study revealed that the greatest proportion of RCTs in neurosurgery did not refer to sample size calculation or power analysis. This result is consistent with previous studies reporting that surgical clinical trials need to improve sample size determination and statistical power reporting,[32-35] and suggests that this issue has remained unimproved over time.

More than half of the RCTs analyzed had no dropouts and half did not lose patients to follow-up. However, 10% failed to report this information. Loss-to-follow-up may contribute for bias in RCTs and previous reviews analyzing RCTs in other surgical indications, indicate a highly variable proportion of patients lost to follow-up.[36-39]

Although nearly 90% of the studies reported the statistical tests used for data analysis, only 24% reported the type of analysis performed (i.e., intent-to-treat or per protocol analysis). Intent-to-treat analysis is commonly recommended, as it provides unbiased estimates of treatment effects.[40] However, it is sometimes difficult to apply, due to the occurrence of missing data[41] and other strategies may have to be used. Therefore, reporting the type of analysis used is critical to ensure a correct interpretation of results.

A small proportion of the analyzed studies (7,4%) mentioned the use of sham interventions as control, among which 34 (3%) referred to surgical interventions. While in surgical RCTs sham-surgery might comprise the ideal comparative treatment, the ethical aspects of subjecting patients to the risk of unnecessary surgery have been discussed. A review of trials using sham surgery as control showed that 80% did not show superiority to non-placebo trials, whereas the occurrence of severe adverse effects was similar between the treatment and control groups.[42] Moreover, another previous study reported that sham surgery often has a low validity due to the existence of various confounding factors.[39] Therefore, although we looked at this topic in the present study, further research is needed to assess the quality of this parameter in neurosurgery trials, regarding its characteristics.

The present study used the Cochrane Risk of bias tool, which is an important measure of a trial's internal validity.[17]

We found that the overall risk of bias decreased over time, with the greatest proportion of trials published in the last decade classified as "Low" risk of bias. However, a considerable proportion of the studies analyzed were classified as "Unclear", which reflects the lack of critical information preventing a proper risk of bias assessment. The proportions of studies classified as "High" and "Unclear" both decreased over time, suggesting that the creation of checklists to improve the quality of RCTs, such as the CONSORT, have been successful to some extent.

Regarding the different risk of bias classification of different methodological aspects, those more frequently classified as "High" were "blinding of subjects and personnel" and "incomplete outcome data". These results are consistent with previous studies assessing trials in other fields of surgery,[5,43] which point out that a low proportion of studies report a correct blinding.

In conclusion, a significant proportion of RCTs in neurosurgery fail to report critical methodological information. Although the risk of bias has decreased over time, there is still room for further improvement, especially regarding design, randomization, blinding and sample size calculation.

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## *CHAPTER 6. SHAM INTERVENTIONS IN NEUROSURGERY*

**This section corresponds to the peer-reviewed manuscript with the reference:**

Gorayeb RP, Forjaz MJ, Ferreira AG, Ferreira JJ. Use of Sham Interventions in Randomized Controlled Trials in Neurosurgery. 2020. J Neurol Surg A Cent Eur Neurosurg. doi: 10.1055/s-0040-1709161.


**ABSTRACT**

**Background:** The use of sham interventions in randomized controlled trials (RCTs) is essential to minimize bias. However, their use in surgery RCTs is rare and subject to ethical concerns. To date, no studies have looked at the use of sham interventions in RCTs in neurosurgery.

**Methods**: This study evaluated the frequency, type and indication of sham interventions in RCTs in neurosurgery. Additionally, RCTs using sham interventions were characterized in terms of design and risk of bias.

**Results**: From a total of 1102 identified RCTs in neurosurgery, 82 (7,4%) used sham interventions. The most common neurosurgical indication was the treatment of pain (67,1%), followed by the treatment of movement disorders and other clinical problems (18,3%) and brain injuries (12,2%). The most used sham interventions were saline injections, both in the spine (31,7%) and peripheral nerves (10,9%), followed by cranial surgery (26,8%), spine surgery (15,8%) and insertion of probes or catheters for sham lesions (14,6%).

In terms of methodology, most RCTs using sham interventions were double-blinded (76,5%), whereas 9,9% were single-blinded, and 13,6% did not report the type of blinding.

**Conclusion:** Sham-controlled RCTs in a neurosurgical indication are feasible. Most aim to minimize bias and to evaluate the efficacy of pain management methods, especially in a spinal indication. The greatest proportion of sham-controlled RCTs involves different types of substance administration routes, with sham surgery being less commonly performed.



**Keywords:** Randomized controlled trials; RCTs; neurosurgery; Bias; Sham

## INTRODUCTION

Double-blind, randomized, placebo-controlled trials are the gold-standard studies to evaluate the causal relationship between treatment and outcome[1,2.]

The use of a placebo control group allows to minimize bias and to evaluate treatment-specific efficacy. While on pharmacology RCTs this often involves the non-invasive administration of an inert substance, in RCTs assessing new surgical techniques or procedures, a sham intervention can be used as control[3].

Sham interventions mimic the actual procedure in every way, with the exclusion of its therapeutic component[4] and have therefore been considered as a more adequate control than no physical intervention or standard medical care, as they allow to clearly distinguish the procedure's efficacy from a placebo response[3].

The use of sham interventions in surgical RCTs is relatively uncommon, mostly due to ethical concerns. However, not only do such concerns lack supporting evidence but there is also increasing acceptance that sham interventions can be performed whenever there is a clinical necessity and there are no alternative trial designs that may respond the same research question [5,6,7].

Apart from the inherent ethical issues, the use of sham interventions in surgical RCTs is limited by funding constraints [8,9], design complexity [8,10] and recruitment difficulty[8]. Therefore, most interventional procedures have been assessed without the use of sham interventions [11]. and, as a result, information regarding the use of sham interventions in RCTs in neurosurgery is scarce.

The aim of this study was to determine the frequency of use of sham interventions in RCTs in neurosurgery. Additionally, it identified the neurosurgical indications and type of sham interventions used in those RCTs and characterized them in terms of design and risk of bias.

## METHODS

*Study design*

This systematic review determined the frequency of RCTs in neurosurgery that used a sham control group and characterized the type of sham interventions used.

*Search strategy*

The total number of RCTs in neurosurgery published between 1900 and December 31, 2013 was determined through a detailed search, which included the following steps: a) open electronic searches on PubMed, the Cochrane Library, and the Centre for Reviews and

Dissemination (CRD) databases, using "RCTs" and "neurosurgery" as keywords; b) a PubMed search using keywords related to neurosurgical clinical entities (i.e., publication type = 'randomized controlled trial' AND (pathology subtype) AND date-publication='1900/01/01':date-publication=2013/12/31), and c) hand-searches on the reference lists of the identified RCTs, systematic reviews and meta-analyses (Figure 1).
Duplications and abstracts were excluded from the total number of retrieved results, leading to the final list of published RCTs.

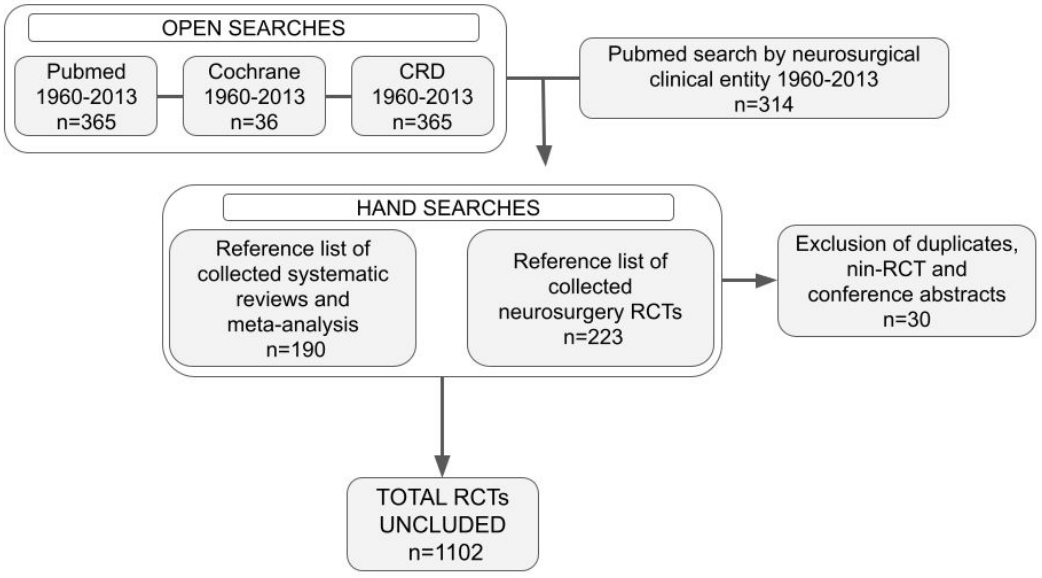


Figure 1. Search strategy followed to identify RCTs in neurosurgery published between 1960 and 2013.

Once the final list was obtained, the search strategies most frequently applied to biomedical databases were assessed regarding the number of RCTs retrieved. These included the keyword searches applied to PubMed, the Cochrane library and the CRD databases, and the Cochrane's High Sensitivity Search Strategy applied to PubMed. Based on the findings of this assessment, the specificity and sensitivity of each of those search strategies were determined.
Among those, RCTs using sham interventions as control were analyzed.

*Data extraction*

Included RCTs were identified by one of the authors (RG), who consulted a second author (JJF) for decision of unclear cases. Inclusion was based on the existence of a control group considered as a sham intervention either by the RCTs' authors, or by us.

Analyzed information included the neurosurgical indication, type of sham intervention, and the most relevant methodological characteristics: type of blinding, type of outcome measured, number of patients included and lost (i.e., either drop-outs due to protocol violation, or participants lost to follow-up), and duration of follow-up. Additionally, each RCT was classified using the Cochrane risk of bias tool (http://methods.cochrane.org/bias/assessing-risk-bias-included-studies), according to which the following methodological aspects were classified with either "High", "Low" or "Unclear" risk of bias: selection bias (i.e., random sequence generation and allocation concealment); performance bias (i.e., blinding of participants and personnel); detection bias (i.e., blinding of outcome assessment); attrition bias (i.e., occurrence of incomplete outcome data); reporting bias (i.e., selective outcome reporting); and other bias (i.e., other sources of bias, such as industry sponsorship). Subsequently, the overall risk of bias was determined for each RCT, according to the most prevalent classification. Trials with equal number of methodological aspects classified as "High" and "Low" risk of bias, received an overall classification of "Medium".

*Data analysis*

The frequency of RCTs in neurosurgery using a sham control group was calculated. Unless stated otherwise, results are presented as number and percentages.

## RESULTS

*Proportion of RCTs with sham interventions*

From the total of 1102 identified RCTs in neurosurgery, 82 (7,4%) included sham interventions and were used for further analysis. The number of published RCTs using sham interventions as control, in relation to the total number of RCTs published per decade is presented in Figure 2. No RCTs using sham interventions were published before 1973.

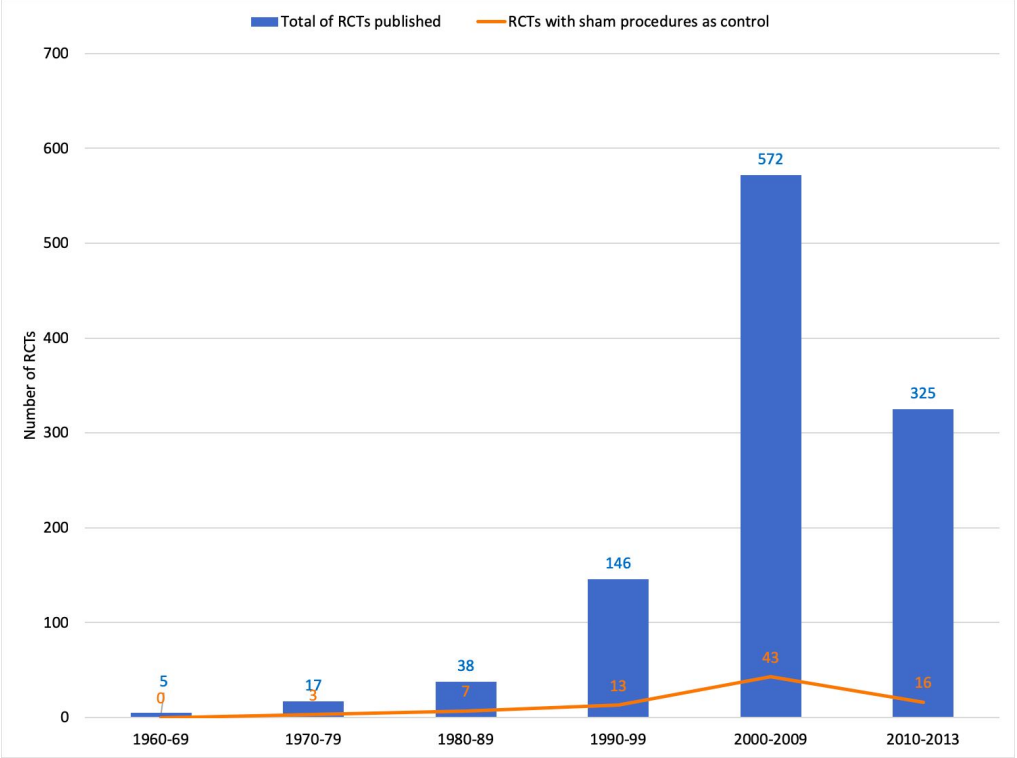


Figure 2. Number of RCTs using sham interventions and total number of RCTs published in each decade. No RCTs using sham interventions as control were published before 1973.

*Neurosurgical indications and type of sham interventions used*

The neurosurgical indications of the analyzed RCTs are presented in Table 1. Most RCTs pertained to the treatment of pain (n=55; 67,1%), among which the greatest proportion was associated with spinal conditions (n=52; 63,4%).

Among the remaining RCTs 15 (18,3%) concerned the treatment of movement disorders and other clinical problems, 10 (12,2%) the treatment of brain injuries and 2 (2,4%) concerned the treatment of vertebral fractures.

| | **N** | **%** |
|---|---|---|
| **Treatment of pain** | **55** | **67,1** |
| Lumbar pain and sciatica | 37 | 45,1 |
| Postsurgical spine pain | 10 | 12,2 |
| Carpal tunnel | 3 | 3,7 |
| Migraine | 3 | 3,7 |
| Cervical pain | 2 | 2,4 |

| | | |
|---|---|---|
| **Treatment of vertebral fractures** | **2** | **2,4** |
| **Treatment of brain injury** | **10** | **12,2** |
| Intraventricular hemorrhage | 3 | 3,7 |
| Aneurysms | 2 | 2,4 |
| Chronic subdural hematoma | 1 | 1,2 |
| Stroke | 1 | 1,2 |
| **Treatment of movement disorders and other clinical problems** | **15** | **18,3** |
| Parkinson's disease | 5 | 6,1 |
| Dystonia | 4 | 4,9 |
| OCD | 3 | 3,7 |
| Tourette syndrome | 2 | 2,4 |
| Depression | 1 | 1,2 |

Table 1. Neurosurgical indications of the RCTs using sham interventions as control. Results presented as numbers and percentages; n=82.

Information regarding the type of sham intervention is presented in Table 2. Most studies (42,6%) involved injections to administer a placebo solution either into the spine (31,7%) or peripheral nerves (10,9%). Cranial surgery was performed in 22 RTCs (26,8%), among which 12 (14,6%) used cranial implant surgery for sham deep brain stimulation, 7 (8,5%) concerned the intraoperative administration of a placebo solution and 3 (3,7%) used sham surgery comprising scalp incision and partial burr holes without dura mater penetration. Spine surgery was performed in 12 RCTs (14,6%), among which 10 consisted of the intraoperative administration of a placebo solution, two consisted of pre- and post-operative administration of a placebo solution (one each). Insertion of probes or catheters for sham lesion was performed in 12 RCTs (14,6%), among which 9 used radiofrequency, 2 used IDET and 1 used percutaneous epidural lysis.

In 24 RCTs (29,3%) the active treatment was offered to the control group at the end of the trial, whereas in 57 RCTs (69,5%) that option was not available.

| | N | % |
|---|---|---|
| **Spine injections of saline** | **26** | 31,8 |
| Intradiscal injection | 9 | 10,9 |
| Intervertebral injection | 5 | 6,1 |
| Epidural injection | 8 | 9,7 |
| Extradural injection | 2 | 2,4 |
| Periradicular injection | 2 | 2,4 |
| **Other saline injections** | **9** | **10,9** |
| Occipital injection | 3 | 3,7 |
| Carpal injection | 3 | 3,7 |
| Sacroiliac injection | 1 | 1,2 |
| Fibular head injection | 1 | 1,2 |
| Intramuscular injection | 1 | 1,2 |
| **Cranial surgery** | **22** | **26,8** |
| Implant surgery for sham stimulation | 12 | 14,6 |
| Intrasurgical administration of placebo solution | 7 | 8,5 |
| Sham surgery | 3 | 3,7 |
| **Spine surgery** | **13** | **15,9** |
| Intrasurgical administration of placebo solution | 11 | 12,2 |
| Preoperative administration of placebo solution | 1 | 1,2 |

| | | |
|---|---|---|
| Postoperative administration of placebo solution | 1 | 1,2 |
| **Probe insertion with sham lesion** | **12** | **14,6** |
| Radiofrequency probe insertion with sham lesion | 9 | 10,9 |
| IDET probe insertion with sham lesion | 2 | 2,4 |
| Catheter insertion with sham lysis | 1 | 1,2 |

Table 2. Type of sham interventions used. Results presented as numbers and percentages; n=82.

*RCTs characteristics*

Among RCTs with sham interventions, most were double-blinded (76,5%), whereas 9,9% were single-blinded and 13,6% did not report the type of blinding used (Figure 3).

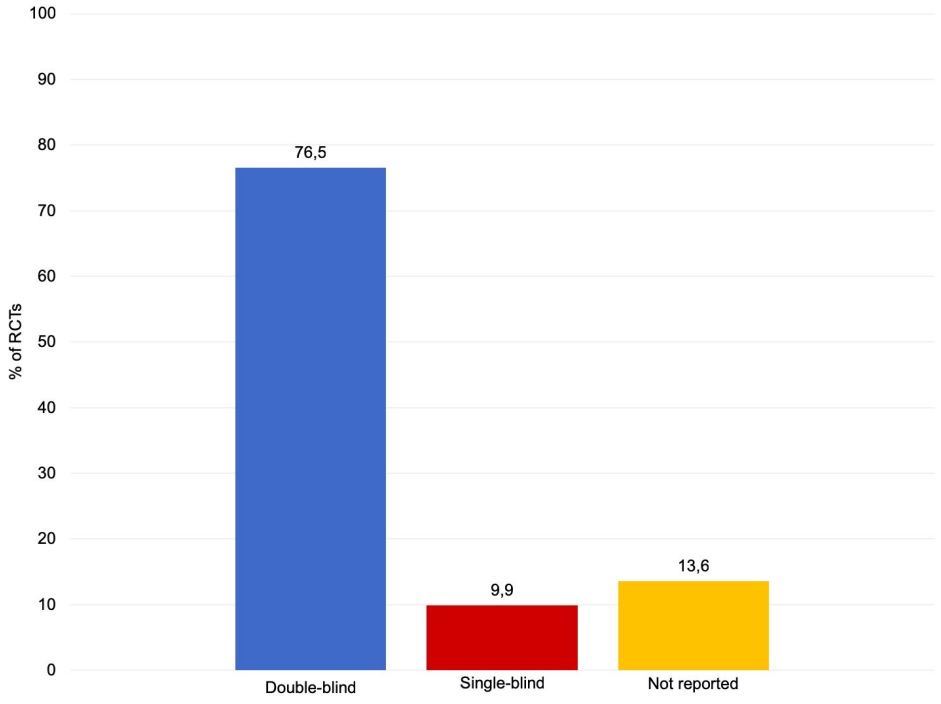


Figure 3. Type of blinding used in RCTs with sham interventions.

Although no direct comparisons can be made, we looked into the sample size, number of dropouts, loss to follow-up and follow-up duration of RCTs with sham interventions in relation to those without sham interventions.

While overall (i.e., among the 1102 RCTs identified), 528 RCTs (47,9%) had between 20-80 participants, 488 (44,3%) had more than 80 participants and 86 (7,8%) had less than 20 participants, among RCTs with sham interventions 45 (54,9%) included between 20-80 participants, whereas 21 (25,6%) included more than 80 and 16 (19,5%) included less than 20. The overall average and maximum number of participants were 122,5 and 2143, respectively, whereas among RCTs with sham interventions the average and maximum number of participants were 72,7 and 403, respectively.

Among RCTs with dropouts, both overall and among RCTS with sham interventions, the highest proportion lost between 1 and 5 participants (13,7% overall vs 21% for RCTs with sham interventions). Among all RCTs, 10,0% did not report that information, whereas among those with sham interventions, all RCTs reported it. Among the RCTs which lost patients to follow-up, overall most lost between 1 and 5 participants (n=148, 13,4%) and 113 (10,3%) did not report that information. Among those with sham interventions, most lost 1-5 patients (n=15; 18,3%) and all reported that information.

Among all RCTs, the average and maximum follow-up duration were 19,6 months and 27 years, respectively, whereas for RCTs with sham interventions the average ad maximum follow-up duration were 9 months and 10 years, respectively.

*Risk of bias*

Information regarding the risk of bias of RCTs with sham interventions is presented in Figure 5. The two methodological aspects more frequently classified with a high risk of bias were "Incomplete outcome data" (27,2%) and "Blinding of patients and personnel" (19,8%), whereas the two methodological aspects more frequently classified with low risk of bias were "Selective outcome reporting" (75,3%) and "Incomplete outcome data" (69,1%).

Regarding the overall risk of bias, the proportions of RCTs classified with low, high and unclear risk of bias were 45,7%, 14,8% and 39,5%, respectively. No RCTs were classified with a medium risk of bias.

## DISCUSSION

The present study focused on the use of sham interventions in RCTs in neurosurgery. Among the 1102 RCTs identified, only 82 used sham interventions as control, with the first being published in 1973. Thereafter, the use of sham interventions increased over time.

Most RCTs using sham interventions studied methods to treat pain, especially pain related to spine conditions, such as disk herniations and sciatica. Among those, the highest proportion tested spine infiltrations of different drugs, using saline as control. Surgical interventions (both spinal and cranial) were used is less than 30% of the studies, and most of them pertained to the intraoperative administration of substances, with sham surgery being rarely used. These results are consistent with the findings of previous reviews reporting a very low use of sham surgery as control. Wartolowska et al.[12] reviewed the use of sham surgery until the end of 2013 and found that it was used in only 53 RCTs, among which 39 were published after 2000. On the other hand, Ciccozzi et al.[1] reviewed the use of sham surgery until May 2015 and reported a total of 52 RCTs. Louw et al.[13] reviewed the use of sham surgery in RCTs in orthopedics, with no time restrictions, finding only 6 results.

The present study looked at all interventions rather than just surgery, which justifies the higher number of RCTs identified.

Most trials using sham interventions as control were double-blinded. The review by Ciccozzi et al.[1] found that 69% of the analyzed RCTs were double-blinded and 31% were single-blinded. In the present study nearly 14% of the analyzed RCTs lacked information regarding the type of blinding used, which makes it difficult to compare the present results with those of previous reviews.

The risk of bias tool is considered an important method to measure a trials' internal validity[14]. Our results show that the methodological aspects more frequently classified with a high risk of bias are "Incomplete outcome data" and "Blinding of patients and personnel", whereas that more frequently classified with low risk of bias is "Selective outcome reporting". These results are consistent with the reviews conducted by Agha et al.[15] and Voineskos et al.[16], which indicate that a low proportion of surgical trials reported a correct use of blinding. Interestingly, Zhai et al.[17] reported that among surgical trials published in major neurology journals, the "Selective outcome reporting" worsened between 2008 and 2013, which is not in line with our findings. In the present study, nearly 15% of RCTs with sham interventions had a high overall risk of bias, reflecting the findings by Ciccozzi et al.[1], who pointed out that the

reliability of sham interventions should be questioned due to the presence of several confounding factors and the lack of information reported.

The results from the present study suggest that, in general, sham-controlled studies have a lower sample size and a higher number of dropouts, which may be related to the shorter follow-up observed. Although RCTs using sham interventions as control are feasible, recruiting participants is a challenge. A placebo controlled-RCT of meniscectomy reported the need to screen 11,9 individuals in order to include one[18], whereas an RCT comparing rehabilitation with early surgery required 5.5 individuals to be screened in order to include one[19]. On the other hand, a placebo-controlled RCT in vertebroplasty for painful osteoporotic fractures, reported that only 6 patients needed to be screened for one to be included[19], suggesting that recruitment difficulties depend on the condition and interventions involved. A study by Swift[20] revealed that, among patients with Parkinson's disease, the willingness to participate in a sham-controlled trial was greatly influenced by the disease severity and lack of standard treatment options.

In the present study only about 30% of the RCTs analyzed offered the active treatment to the control group at the end of the trial. Making this option available in all trials where the treatment under study proves effective, may facilitate participant recruitment.

## Conclusion

Despite the challenges faced by sham-controlled RCTs, the present study indicates that sham interventions in neurosurgery are feasible, in particular when they target pain management methods, and most consist of injections and infiltrations of different substances aiming to treat spinal conditions.

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## Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with financial interest.

## Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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## *CHAPTER 7. GENERAL DISCUSSION*

Randomized controlled trials (RCTs) are considered the best studies to evaluate the efficacy of new therapeutics, as they allow to dramatically decrease the possibility of bias through their main basic features: inclusion of a control group, randomization and blinding.

However, the design and performance of RCTs are limited by time, financial and recruitment constraints, and/or other sources of bias such as poor allocation concealment, absence or incorrect use of blinding, missing data, lack of intention-to-treat analysis and competing interests.

In the specific case of neurosurgery, RCTs face the additional challenges of patient inclusion, surgical selection bias, inclusion of an appropriate control group, perceived lack of equipoise and technical expertise. This leads to many innovative surgical procedures being introduced in the form of case-series and adopted into practice without a proper, scientific evaluation.

The present thesis aimed to determine the current scenario of RCTs in neurosurgery, regarding four main aspects: sources of knowledge supporting therapeutic decision-making; RCTs accessibility through widely used electronic search strategies; RCTs design and reporting quality and the frequency of inclusion of a sham control group.

The first study showed that, when questioned about the basis for their therapeutic decisions, neurosurgeons provide ambivalent answers; although they acknowledge the importance of evidence-based medicine, they tend to rely more on their own experience than on scientific literature to support clinical decisions. This tendency was found to be stronger among neurosurgeons with over 10 years of experience, while those with less than 10 years of experience tended to value EBM more. Such findings are consistent with a recent review by Simons et al. (2018), which showed that specific training in evidence-based medicine improved short-term knowledge and skills among doctors, but did not influence long-term knowledge, attitudes or clinical practice. This suggests that clinical decision making among neurosurgeons is mostly based on ‘eminence-based’ (LE HP, 2016) rather than evidence-based medicine, which has been shown to occur also in other medical fields (Gadjradj et al., 2017; Massey et al., 2013; Hoefte et al., 2016; Hoeft et al., 2017).

Interestingly, although experience was reported as the most common basis of clinical decisions, most respondents stated their willingness to change their usual practice in order to achieve better outcomes and less severe complications. The main reasons provided for being

unwilling to change the usual practice were the lack of scientific evidence to support the new techniques, and their learning curves.

While most neurosurgeons acknowledged the need to implement guidelines and protocols, less than half of the respondents stated to have them in place. Recent studies have pointed out that the publication of guidelines in neurosurgery occurs slowly compared to other surgical fields, although it has become increasingly common over that past few years (Ducis et al., 2016, Mertens et al, 2018). Such studies also highlight the need for surgical decision-making to be approached from a more unified and systematic manner (Gunaratnam and Bernstein, 2018).

Another finding of this study was that when neurosurgeons resorted to the scientific literature, they used mostly the information provided by scientific abstracts and internet searches, and that half of the respondents were unfamiliar with the interpretation of scientific concepts present in the relevant literature. While this study targeted only Brazilian neurosurgeons, consistent findings have been provided by international studies, which report a general difficulty to critically read the medical literature (Esene et al., 2016). Such difficulty has been recognized as a major setback of medical education (Grimes and Schuls, 2002), which overlooks research as an important part of patient care.

Overall, this study highlights the need to implement guidelines and or recommendations that support therapeutic decision making in neurosurgery.

The second study revealed that most published RCTs in neurosurgery cannot be easily identified through commonly used searches on electronic databases. No single electronic search strategy could retrieve the total number of published RCTs in neurosurgery, which could only be determined using a combination of different search strategies applied to several databases. Such low performance of search strategies was found to be related with poor indexing, particularly regarding the information provided by the studies' title and abstract. Similar findings were previously reported by Kiehna et al (2010) for RCTs in neurosurgery published between 2006 and 2007, suggesting that similar indexing limitations persisted up to our study's endpoint (December 31 2013).

Searches on PubMed were found to have a higher sensitivity and specificity than those performed on the Cochrane library and the CRD, which may be related with the number of articles indexed in each of those databases.

Surprisingly, although the Cochrane's High Sensitivity Search Strategy (HSSS) is considered as the best electronic search tool, it was found to have a poorer performance than open searches on PubMed. Even though the Cochrane's HSSS is commonly used as a tool to identify RCTs for systematic reviews, recent studies have found that it may not be the most sensitive search strategy, missing several relevant studies, mainly due to lack of relevant information on the title and abstract (Cooper et al., 2019)

The fact that most developed search filters rely on the reported methodological information (McKibbon et al., 2009), the results from this study reflect inadequate indexing and methodological report of neurosurgical RCTs, thereby raising the need to investigate the quality of methodological reporting in neurosurgery RCTs.

This study looked into RCTs in neurosurgery published until the end of 2013. Further research is needed to investigate how this issue has evolved over time.

The third study revealed that the number of published RCTs in neurosurgery has increased over the years, with most investigating spine conditions and related treatments, followed by cranial surgery. Importantly, the great majority of published RCTs lacked critical information such as the type of study design (lacking in 90%of all RCTs), information on blinding and the randomization method (both lacking in 60% of RCTs), and type of statistical analyses performed (lacking in 76% of RCTs). Such findings are consistent with reports in other fields of surgery, such as otolaryngology (Banglawala et al., 2015), plastic surgery (Voineskos et al., 2016) and general surgery (Balasubramanian et al., 2006), where RCTs have been found to be of suboptimal quality. This study therefore highlights an urgent need to improve the methodological reporting of RCTs in neurosurgery.

While previous studies have questioned the quality of neurosurgical RCTs (Vranos et al., 2004; Kiehna et al., 2011; Mansouri et al., 2016), a recent review revealed that it is improving over time, with a greater proportion of recent RCTs reporting larger sample sizes and power calculations (Azad et al., 2018). Azad et al. also found that RCTs with larger sample sizes are more likely to report critical design information such as the method of randomization and allocation concealment.

Consistently, our study revealed that the overall risk of bias decreased over time, although a considerable proportion of the studies analyzed were classified as "Unclear", which reflects a lack of critical methodological information, thus poor reporting quality. The main contributors for high risk of bias were inadequate blinding of subject/personnel and incomplete outcome data. This result is consistent with findings in other fields of surgery. For example, Huttner et

al (2018) reviewed the quality of RCTs in plastic surgery and found that, despite an overall improvement over the last years, a high risk of bias persists in terms of blinding.

Given the challenges inherent to surgical RCTs, progress in neurosurgical interventions is mostly guided by case studies and professional experience. The need to increase the number of RCTs in this field was previously raised by Rothoerl et al (2003) and later by Yarascavitch (2012), both pointing out the lack of high-level evidence in the neurosurgical literature.

In summary, a significant proportion of RCTs in neurosurgery fail to report critical methodological information. Although the risk of bias has decreased over time, there is still room for further improvement, especially regarding design, randomization, blinding and sample size calculation.

It is, therefore, urgent to encourage adherence to publication guidelines, such as CONSORT or the Cochrane RoB, which can be achieved by improving post-graduate training, increasing the reporting standards of scientific journals by means of a rigorous peer-review.

On the other hand, the methodological aspects of RCTs, in particular those pertaining to blinding, randomization, and sample size calculation should be improved through specific training and ensured by a higher rigor during peer-review.

The fourth study looked into the use of sham procedures as control in neurosurgery RCTs. We found that sham procedures in neurosurgery are feasible, although only 7.4% of RCTs used a sham intervention as control. Among those, most investigated methods to treat spine-related pain, especially spinal infiltrations of various substances, with only 30% of RCTs using surgical procedures.

Levack et al. (2019) recently reviewed how the inclusion and type of control groups was managed in Cochrane reviews of neurorehabilitation and found that the clinical trials included in those reviews were highly variable in terms of control group inclusion; most trials compared the experimental intervention with another active intervention, whereas placebo or sham interventions were rarely used.

The inclusion of control groups in RCTs ensures that the results obtained are due to the investigated therapy, rather than to non-specific confounding factors (Brigham et al., 2009). Control groups allow to estimate effect sizes by taking potential sources of bias into consideration. However, when control participants also receive active therapies, the reported effect sizes may not reflect the therapy's actual value (Levack et al., 2019), thus sham procedures allow a more precise evaluation of the treatment effect (Schulman et al., 2017).

However, they are rarely used in surgical trials, especially due to recruitment difficulties (Frobell et al., 2007; Swift, 2012; Hare et al., 2014).

Sham procedures have often been considered as a source of ethical controversy (Horng and Miller, 2003). While they may carry some advantages for the patients included in control groups, such as allowing them to receive standard care at no cost, providing the therapeutic procedure at a later stage should it be proven effective, and avoiding them to undergo a new procedure that can potentially be harmful (Schulman et al., 2017), sham procedures involve potential unforeseeable risks with no significant benefits.

On the other hand, sham procedures are considered to increase the scientific validity of RCTs (Albin, 2005; Swift et al., 2013; Miller, 2004). A review of clinical trials in tendinopathy (Challoumas et al., 2019) comparing surgical treatment with sham surgery and conservative treatment (physiotherapy) found that, while surgery appeared to have superior results to conservative treatment, there were no outcome differences between surgical treatment and sham surgery. Similar results were reported by Kroslak and Murrell (2018) and by Beard et al (2018), who attributed this difference to the occurrence of a surgical placebo effect.

While the use of sham interventions in RCTs in neurosurgery is challenging, this thesis shows that they are feasible and especially adequate to evaluate pain management methods.

## *CHAPTER 8. FINAL REMARKS*

The present thesis demonstrates that, although RCTs constitute the highest level of evidence, in the field of neurosurgery they are not currently the main source of knowledge underlying therapeutic decision-making, as most neurosurgeons, particularly those with over 10 years of experience, prefer to rely on their own expertise.

Additionally, RCTs in neurosurgery are not easily accessible through commonly used search strategies applied to electronic databases, which is mostly due to poor quality of reporting and indexing.

While the number of published RCTs in neurosurgery has increased over the past few years, it remains low when compared to other medical fields, especially due to the challenges inherent to their design and performance. Moreover, published RCTs in neurosurgery lack quality in terms of experimental methodology, and they are poorly reported, with missing information on several critical design aspects.

Although the inclusion of sham procedures in neurosurgical RCTs is feasible, very few include such procedures, which limits the clinical relevance of the estimated effects.

This thesis puts forward an urgent need to improve the methodological quality, reporting and indexing of RCTs in neurosurgery, which may be achieved through the implementation of guidelines, adequate training and rigorous peer-review.

A better understanding of methodological aspects, placebo effect, sham surgery, increased benefits of a control group and rigorous statistical analysis can improve the quality of everyday clinical and surgical practice for the vast majority of neurosurgeons.

Also, concerning neurosurgical research, the perceived lack of guidance on EBM and direction of studies towards multicentre RCTs should increase to be addressed by major schools and societies.

As a researcher, I consider that the identification of what needs to be improved is clear. Nonetheless, in my opinion, it involves, in some cases, altering the basic rationale of surgeons. So making the transformation effective and enduring remains a daunting, challenging task, and I perhaps could futurelly be content with continuing with projects on this line of thought.

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