Innovation in neurosurgery: Evaluation of neurosurgical innovation, related ethics, and solutions

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Randomized controlled trials comparing surgery to conservative management in neurosurgery: a systematic review

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***Introduction**: A randomized controlled trial (RCT) remains the pinnacle of trial design. However, RCTs in neurosurgery are rare, especially those that compare surgery to conservative treatment, and their relevance and applicability has been questioned. The aim of this study is to evaluate the clinical impact and final results of RCTs in neurosurgery, using trials that compare surgery to conservative management. **Methods**: From 2000, PubMed and Embase databases and four trial registries (ClinicalTrials.gov, EudraCT, ISRCTN, and ICTRP) were searched for RCTs comparing a surgical procedure with conservative management. RCTs were evaluated for study design, funding, adjustments to reported outcome measures, accrual of patients, and clinical impact. **Results**: 82 individual RCTs were identified in the literature (40 spinal, 19 vascular, 11 functional, 10 peripheral nerve, and 2 oncological). 84 RCTs were found to be registered of which some are ongoing. Trial registration rate*

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differed per subspecialty. Funding was mostly from non-industry institutions (58.5%), but 25.6% of RCTs did not report funding sources. 63.4% of RCTs reported a favourable outcome for surgery, compared to 3.7% for conservative treatment. Primary and secondary outcome measures were changed in 13.2% and 34.2% of RCTs respectively and varied by subspecialty. 41.9% of RCTs subtracted ≥10% of the anticipated accrual of patients and 12.9% of RCTs added ≥10%. 7.3% of registered RCTs were terminated, most commonly due to slow recruitment. Subspecialty, registration, funding, masking, population size, changing outcome measures, and Jadad score were not significantly associated with a reported benefit of surgery. ***Conclusions****: RCTs comparing surgical to conservative treatment remain rare in neurosurgery and often find a benefit for surgical treatment. Changes to outcome measurements and anticipated accrual are not uncommon. Half of the trials are registered, and funding sources are not always reported. Successfulness of future neurosurgical RCTs could be improved by trial registration prior to patient inclusion and pilot studies.*

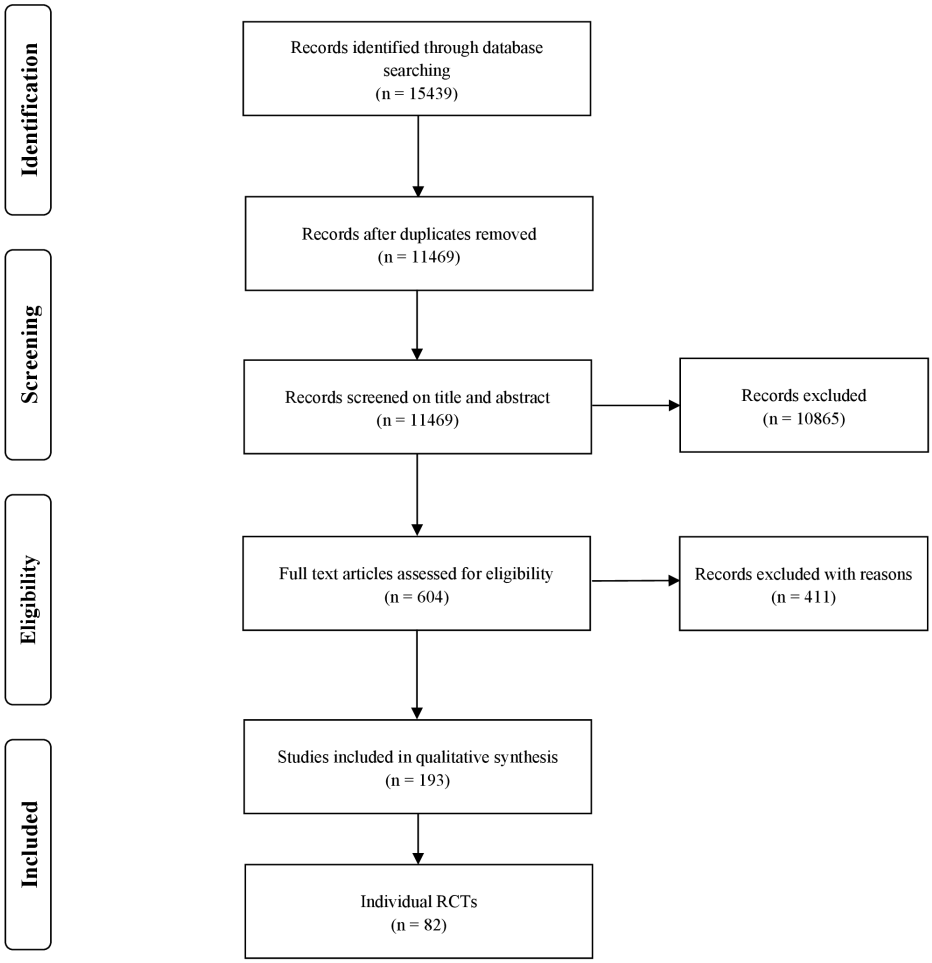
Introduction

Most neurosurgical procedures are the result of continuous improvement and evolvement of existing procedures and are rarely compared with conservative management in a methodologically sound manner to prove true undisputed benefit. The randomized controlled trial (RCT) is commonly regarded as the pinnacle of trial design and is thought to produce the highest quality evidence.[16] Conducting a randomized controlled trial in neurosurgery could be regarded as problematic due to problems with e.g. patient inclusion, defining relevant outcomes, lack of equipoise, and providing a conclusive answer.[17, 23] Perhaps partially as a result, RCTs in neurosurgery are relatively infrequently conducted and their quality has been suggested to be poor.[2, 9, 13] This may even be more the case when a neurosurgical procedure is compared to conservative management, rather than a different neurosurgical procedure or use of a medical device.[4, 8, 17]

Evaluations of RCT quality in other surgical fields have also identified a relatively low quality, as seen in ophthalmologic surgery and vascular surgery.[3, 22] However, others have suggested that the quality of surgical RCTs has improved over the years.[1] Questions remain regarding trial quality, reporting, and if trial design affects the outcome of a surgical benefit in neurosurgical RCTs.

In this systematic review, the literature is evaluated for neurosurgical RCTs that compare a neurosurgical procedure with conservative management. The aim of this review is to evaluate neurosurgical RCT design, quality, conduction, and reported outcomes. An additional aim is to identify which trial characteristics are associated with a reported surgical benefit. Moreover, this review will evaluate how often predefined outcome measures and accrual of patients are changed, and how the latter may influence trial findings.

Figure 4.1: Flowchart Depicting Study Selection



Methods

A systematic search was performed in both Pubmed and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, [20] in order to identify all potentially relevant trials as of January 2017. The search string was drafted with the help of a professional librarian using search terms related to 'neurosurgery' together with specific neurosurgical procedures and synonyms of 'randomized trial'. The databases were only searched for RCTs published after 2000. The exact search syntaxes for Pubmed and Embase are shown in **Supplementary Table 4.6**. Studies were included if they described data from a randomized controlled trial that compared any form of surgery to a non-surgical group.

Papers were excluded that 1) were not randomized 2) did not have a conservative treatment arm 3) were not part of a trial of which the results were already published 4) had no full text was available 5) were not written in English, Dutch, German, or French. The initial review was carried out by four independent authors (EM, IM, JS, AD). Disagreements were solved through discussion, in which one additional author was involved (MB). The amount of published papers per trial was recorded, including design or protocol and reported pilot studies or early results. Data were extracted from the first published paper on main results. These included a) trial start and end date b) neurosurgical subspecialty c) countries involved d) number of countries involved e) number of participating centers f) funding source (non-industry, industry, or not reported) g) total amount of anticipated and included patients h) patients per study arm i) masking j) and if the outcome favored surgery or conservative treatment. Scopus was consulted for the number of times the first results of the study were cited. The impact factor of the journal was determined as the journal's indicated impact factor of 2016. Jadad scales were calculated for each trial to measure study quality.[5]

Table 4.1: RCT demographics per subspecialty

		Total	*Spinal*	*Vascular*	*Functional*	*PNS*	*Oncological*
No. Trials		82	40 (48.8%)	19 (23.2%)	11 (13.4%)	10 (12.2%)	2 (2.4%)
Registered		38 (46.3%)	15 (37.5%)	13 (68.4%)	5 (45.5%)	5 (50%)	0 (0%)
No. Publications	Median (IQR)	2 (1-3)	2 (1-4)	1 (1-2)	2 (1-2)	1 (1-2)	1 (1-1)
No. Centers	Multicenter	48 (58.5%)	22 (55%)	16 (84.2%)	7 (63.6%)	2 (20%)	1 (50%)
	Single-centered	30 (36.6%)	15 (37.5%)	2 (10.5%)	4 (36.4%)	8 (80%)	1 (50%)
	Unknown	4 (4.9%)	3 (7.5%)	1 (5.3%)	0 (0%)	0 (0%)	0 (0%)
	Median (IQR)	3.5 (1.0-13.0)	3.0 (1.0-9.0)	18.5 (6.0-47.3)	3.0 (1.0-8.5)	1.0 (1.0-1.0)	23.5 (12.3-34.8)
No. Countries	Median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-7.8)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	4.0 (2.5-5.5)
Duration (months)	Median (IQR)	42 (27.8-68)	42 (35.5-60)	63 (21.8-90.8)	47 (39.8-58)	18 (12.5-36.5)	*NA*
No. Patients	Total (Median)	95 (50.0-174.5)	98 (62.8-177.5)	112 (35.0-300.0)	48 (35.0-118.0)	108 (51.8-119.0)	61.5 (41.8-81.3)
	Sx (Median)	47.5 (26.0-87.0)	50 (30.3-87.3)	61 (21.0-174.8)	26 (15.8-38.8)	53.5 (18.3-59.5)	30.5 (20.8-40.3)
	Non-Sx (Median)	47 (24.0-82.0)	49 (30.3-70.8)	72.5 (19.3-163.8)	21.0 (15.8-39.0)	54 (30.3-59.8)	31.0 (21.0-41.0)
Masking	Double Blind	7 (8.5%)	3 (7.5%)	0 (0%)	4 (36.4%)	0 (0%)	0 (0%)
	Single Blind	26 (31.7%)	8 (20%)	9 (47.4%)	5 (45.5%)	4 (40%)	0 (0%)
	Open Label	49 (59.8%)	29 (72.5%)	10 (52.6%)	2 (18.2%)	6 (60%)	2 (100%)
Outcome	Surgical	52 (63.4%)	23 (57.5%)	13 (68.4%)	8 (72.7%)	8 (80%)	0 (0%)
	Conservative	3 (3.7%)	2 (5%)	1 (5.3%)	0 (0%)	0 (0%)	0 (0%)
	No Difference	27 (32.9%)	15 (37.5%)	5 (26.3%)	3 (27.3%)	2 (20%)	2 (100%)
Funding	Non-Industry	48 (58.5%)	25 (62.5%)	11 (57.9%)	7 (63.6%)	5 (50%)	0 (0%)
	Industry	13 (15.9%)	7 (17.5%)	1 (5.3%)	4 (36.4%)	0 (0%)	1 (50%)
	Not reported	21 (25.6%)	8 (20%)	7 (36.8%)	0 (0%)	5 (50%)	1 (50%)
No. Citations	Median (IQR)	95 (21.8-296.0)	127.5 (22.8-286.0)	135 (30.5-331.0)	258 (64.5-1058.0)	48 (3.3-86.5)	40 (26.0-54.0)
Impact factor	Median (IQR)	6.1(2.4-39.3)	3.4 (2.1-32.1)	23.5 (3.6-44.0)	23.5 (8.9-48.6)	8.2 (3.0-15.0)	3.5 (3.5-3.5)
Jadad	Median (IQR)	3 (2-3)	2.5 (2-3)	3 (2-3)	3 (2-4)	3 (1.25-3)	1 (1-1)

Abbreviations:IQR: interquartile range, mo: months, No.: number of, PNS: peripheral nerve surgery, SD: standard deviation, Sx: surgical arm

Four trial registries (ClinicalTrials.gov, EudraCT, ISRCTN, and ICTRP) were searched as well with synonyms of 'neurosurgery'. All randomized trials investi-

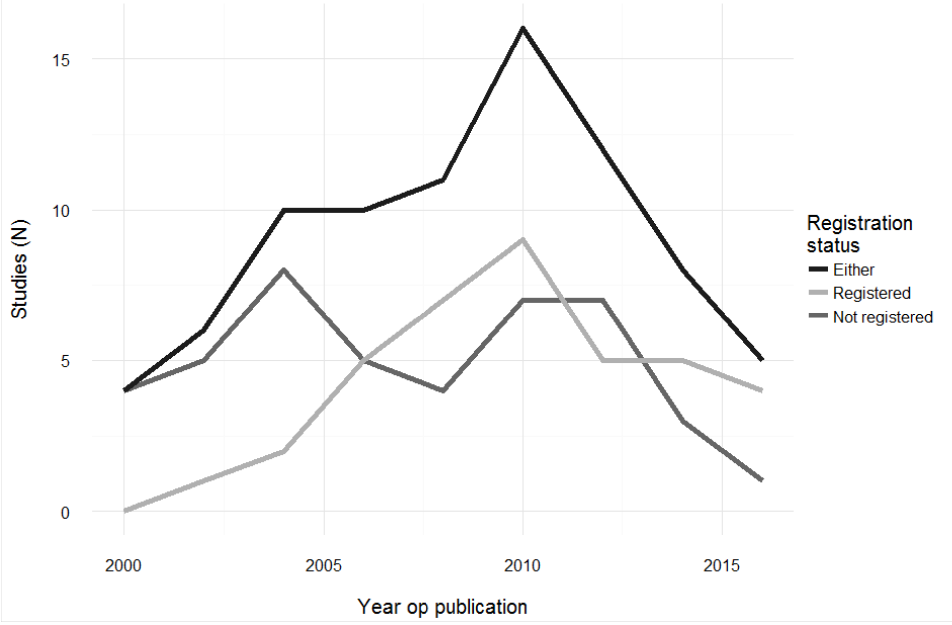
gating a neurosurgical treatment to a non-surgical treatment were included. Registry data and published protocols were used to determine if and what changes were made to primary and secondary outcome measurements in comparison to first published main results. Additionally, the anticipated accrual of patients was evaluated for whether it was met or surpassed. The current status of registered trials was also noted.

Methodological characteristics (as listed above) were evaluated for association with surgical or non-surgical reported benefit by univariate logistic regression. Statistical analyses and data visualization were conducted using R version 3.4.3 (R Core Team, 2017).

Results

After removal of duplicates, a total of 11469 citations were identified in Pubmed and Embase databases. 604 potentially relevant articles were selected through title/abstract screening, of which 193 articles were selected for qualitative synthesis after full-text screening (**Figure 4.1**). A total of 82 individual RCTs were identified (**Table 4.1**). A total of 84 RCTs were found registered in one of the registries searched.

Figure 4.2: Registration Status over Time.



Study characteristics

Of all randomized trials 40 (48.8%) were in spine, 19 (23.2%) vascular, 11 (13.4%) functional, 10 (12.2%) peripheral nerve, and 2 (2.4%) oncological subspecialty (**Table 4.1**).

The latter only included pituitary tumors. Overall, a median of 2 papers (IQR: 1-3) were published per trial, with spinal (2, IQR: 1-4) and functional (2, IQR: 1-2) subspecialties having most publications per RCT. Trial registration was highest in vascular neurosurgery (68.4%) and lowest in spine surgery (37.5%). Twenty RCTs were multicenter, but this was only the case in 20% of peripheral nerve surgery trials (n = 2). Median time to trial completion was 42 months (IQR: 27.8-68.0). RCTs in peripheral nerve surgery had the lowest median time to study completion (18 months, IQR: 12.5-36.5). Overall, median number of patients included in an RCT was 95 (IQR: 50.0-174.5), with relatively smaller populations in functional neurosurgery trials (48, IQR: 35-118). Study arms were generally evenly distributed (**Table 4.1**). Most trials were open label (59.8%) whereas double blind trials were relatively rare (8.5%). Double blind trials were most common in functional neurosurgery (36.4%). Funding was usually from non-industry parties (58.5%). However, the funding was not reported in 25.6% of RCTs. Median Jadad scores were 3 (IQR: 2-3). Trial registration rate seems to increase just a little over time (**Figure 4.2**).

Factors associated with trial outcome

The majority of trials reported a favorable outcome for surgical intervention (63.4%) (**Table 4.1**). Only 3.7% of all trials reported a beneficial effect of the non-surgical intervention, while the rest (32.9%) did not find any statistical differences. Only high Jadad scores (≥4) were associated with no surgical benefit (OR: 0.10, 95%-CI: 0.01-0.89). None of the other trial characteristics showed a significant relationship to an outcome favoring surgical treatment (all p-values > 0.05, **Table 4.2**).

Changes in primary and secondary outcome measures

Only registered trials (n = 38) were available for assessment of changes in primary and secondary outcome. 13.2% of these RCTs changed their primary outcome measurement between registration and publication (n = 5, **Table 4.3**). 60% of these changes were simple changes to the primary outcome measure (n = 3), 20% added a primary outcome measure (n = 1), and 20% removed one of the primary outcome measures (n = 1, **Table 4.3**). Secondary outcome measures were changed in 34.2% of all RCTs (n = 16). 50% were simply changed (n = 8), 37.5% had an additional secondary outcome measure (n = 6), and 12.5% removed one or more of their secondary outcome measures (n = 2).

Trial continuation and anticipated

accrual of patients 65.9% of registered RCTs were completed and 26.8% was still ongoing (**Table 4.4**). 7.3% of RCTs were indicated as terminated. This was most commonly due to slow recruitment or meeting a pre-specified futility boundary. The initial anticipated accrual was lowered by more than 10% in 41.9% of all RCTs. The accrual was diminished by 58.5% on average (SD: 25.1%). In 12.9% of trials, initial estimated accrual surpassed 110% of planned patient enrollment (mean added percentage: 41.2, SD: 36.0%).

Table 4.2: Univariate Analysis of Trial Outcome

		No Surgical benefit (N = 30)	*Surgical benefit (N = 52)*	*OR (95%-CI)*	*P-value*
Subspecialty (%)	Spinal	17 (56.7)	23 (44.2)	Ref.	
	Vascular	6 (20.0)	13 (25.0)	1.60 (0.52-5.35)	0.42
	Functional	3 (10.0)	8 (15.4)	1.97 (0.49-10.0)	0.36
	PNS	2 (6.7)	8 (15.4)	2.96 (0.64-21.3)	0.20
	Oncological	2 (6.7)	0 (0.0)	*NA*	
Registered (%)	Not registered	16 (53.3)	28 (53.8)	Ref.	
	Registered	14 (46.7)	24 (46.2)	0.98 (0.40-2.43)	0.96
Funding (%)	Non-industry	20 (66.7)	28 (53.8)	Ref.	
	Industry	5 (16.7)	8 (15.4)	1.14 (0.33-4.26)	0.84
	Unknown	5 (16.7)	16 (30.8)	2.29 (0.75-7.92)	0.16
Multicentered (%)	Singlecenter	9 (30.0)	21 (40.4)	Ref.	
	Multicenter	20 (66.7)	28 (53.8)	0.60 (0.23-1.58)	0.30
	NA	1 (3.3)	3 (5.8)	1.29 (0.12-14.09)	0.84
Masking (%)	Open label	16 (53.3)	33 (63.5)	Ref.	
	Single blind	9 (30.0)	17 (32.7)	0.92 (0.34-2.56)	0.86
	Double blind	5 (16.7)	2 (3.8)	0.19 (0.03-1.01)	0.07
Number of patients (%)	<100	13 (43.3)	29 (55.8)	Ref.	
	≥100	17 (56.7)	23 (44.2)	0.61 (0.24-1.49)	0.28
Change in primary outcome measure (%)	No change	14 (46.7)	19 (36.5)	Ref.	
	Change	1 (3.3)	4 (7.7)	2.95 (0.38-61.1)	0.36
	Unknown	15 (50.0)	29 (55.8)	1.42 (0.56-3.64)	0.46
Change in secondary outcome measure (%)	No change	8 (26.7)	14 (26.9)	Ref.	
	Change	5 (16.7)	9 (17.3)	1.03 (0.26-4.34)	0.97
	Unknown	17 (56.7)	29 (55.8)	0.97 (0.33-2.77)	0.96
Jadad (%)	Jadad <3	11 (36.7)	27 (51.9)	Ref.	
	Jadad ≥3	19 (63.3)	25 (48.1)	0.54 (0.21-1.33)	0.18
	Jadad <4	25 (83.3)	51 (98.1)	Ref.	
	Jadad ≥4	5 (16.7)	1 (1.9)	**0.10 (0.01-0.89)**	**0.01**

Legend: Abbreviations: OR: odds ratio

Table 4.3: Changes in Primary and Secondary Outcome Measures

		Percentage
Change Primary Outcome	Changed	60%
	Added	20%
	Removed	20%
Change Secondary Outcome	Changed	50%
	Added	37.5%
	Removed	12.5%

Academic impact

The median number of citations per study was 95 (IQR: 21.8-296.0). Peripheral nerve surgery and oncological trials had the lowest median number of citations (48, IQR: 3.3-86.5, and 40, IQR 26.0-54.0 respectively, **Table 4.5**). Median impact factor was 6.1 (IQR: 2.4-39.3). Functional neurosurgery trials had the highest median impact

factor at 23.5 (IQR: 8.9-48.6).The median number of citations and impact factor did not differ for trial outcome overall ($p > 0.05$). Post-hoc analyses also did not show any significant difference in number of citations or impact factor between two trial outcomes (all $p > 0.05$).

Figure 4.3: Changes Made in Primary and Secondary Outcome Measures

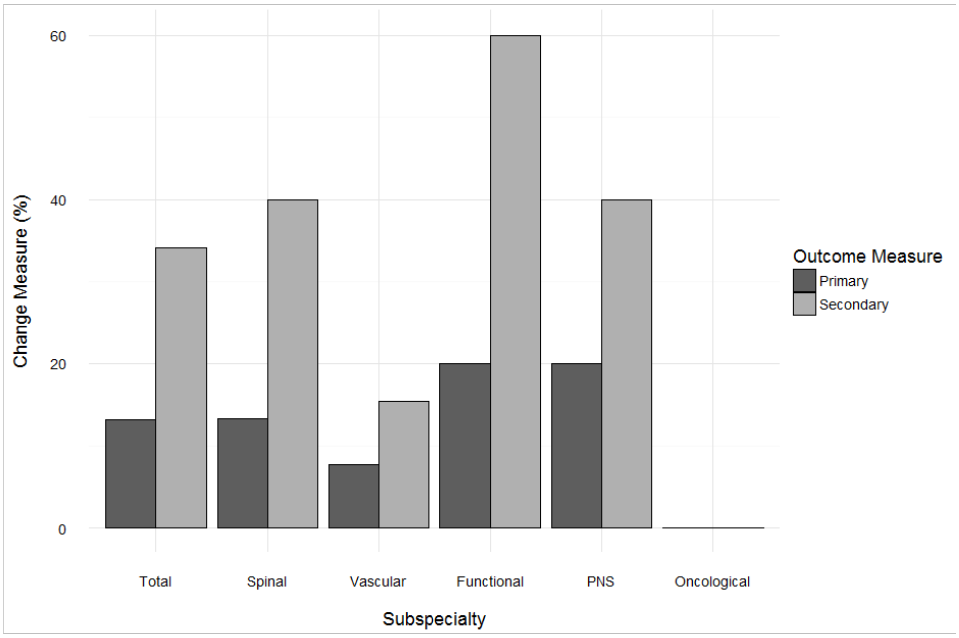


Table 4.4: Trial Registration Data

		Percentage
RCT Status	**Completed**	65.9%
	Active	26.8%
	Terminated	7.3%
Accrual Patients	**Subtracted >10%**	41.9%
	Mean (SD)	58.5% (25.1)
	Added >10%	12.9%
	Mean (SD)	41.2% (36.0)

Table 4.5: Average Academic Impact per Outcome

	Citations Median (IQR)	*P-value*	*Impact Factor Median (IQR)*	*P-value*
Surgical	103.0 (19.5-331.5)	0.33*	6.1 (2.3-44.0)	0.73*
Non-surgical	119.0 (0-NA)		2.1 (2.1-NA)	
No difference	72.0 (24.0-301.0)		5.8 (2.4-26.5)	

Discussion

The aim of this study was to evaluate trial outcomes in recent neurosurgical RCTs comparing surgery to conservative treatment. The authors of the identified RCTs are to be applauded as many trials reported a protocol, registered their trial, and published their protocol. However, this study identified several challenges common among neurosurgical RCTs. Trial outcomes favoring conservative treatment are rarely seen, with 63.4% of RCTs in favor of surgery, and hardly ever was surgery found to be inferior. Funding sources were not reported consistently among all studies identified and many trials were not registered. Changes to primary or secondary outcome measures occurred frequently, but were not shown to influence whether surgery was found to be superior to a surgical procedure. The overall quality of the identified studies based on the Jadad score could be considered poor. Nevertheless, most studies still had a considerable academic impact.

Trial registration and outcome measurement

Differences between registered and published outcomes are suggested to be common among RCTs and were not suggested to be the result of funding sources, which is similar to our study.[7] One study that evaluated outcome reporting among 51 surgical RCTs found that registration is often omitted and primary and secondary outcome measures are often changed, which is also similar to our findings in neurosurgery.[18] A second study among surgical trials showed that 91.7% of trials that changed outcome measures published significant results.[10] Trials in cardiology, rheumatology, and gastroenterology were also found to regularly change outcome measures, which had a significant association with finding a significant outcome.[15] Regardless of how the results of RCTs are produced, one study among RCTs in spine surgery indicated that statistical findings could be considered fragile as the addition of only few events or non-events would have changed the significance of the reported finding.[2]

Trial quality

One study evaluated trial quality among 61 neurosurgical RCTs.[13] They found that the median CONSORT score[19] was 36, what could be considered to be low. Median Jadad scores were less than 3, which is similar to the findings in this study. The study also identified that trials that evaluated surgical procedures met their targets less often than trials that evaluated drugs or medical devises, which was not evaluated in our study. This may implicate that conducting a trial for surgical procedures is

more difficult but may also be the result of bias. A second study that evaluated 27 neurosurgical RCTs found a mean CONSORT score of 41 and a mean Jadad score of 3.42, again similar to our findings.[9] This study also identified that studies published in high impact journals had higher mean CONSORT and Jadad scores, which could implicate that higher impact journals demand higher quality journals and reporting.[9] Findings of this study, however, indicate that the finding of a surgical benefit does not affect academic impact.

Strengths and limitations

This is the first study that sought to evaluate in neurosurgical RCTs comparing a surgical procedure to conservative management which trial characteristics were associated with the identification of a surgical benefit. Both MEDLINE search engines and trial registries were extensively evaluated. The findings provide a valuable insight into the frequency of trial cessation, adjustment of trial design, and quality of reporting, which may provide useful insights for future neurosurgical RCTs.

There are also several limitations to this study. The search engines and registries only provided a relatively small number of RCTs. There is a possibility that trials that were not registered or reported were not identified, which limits the true implications of the findings in the analysis. This may be why only a very low number of studies were identified that found a neurosurgical procedure to be associated with inferior outcomes. Only RCTs published after 2000 were included, which may further limit the number of trials included. Analysis to determine which trial characteristics may be associated with a surgical benefit was complicated because only a minority of the published trials had also been registered and had their protocol available. Therefore, it was not possible to evaluate whether protocols were changed for unregistered studies, which may have provided additional valuable insights. This study is also limited by the sole inclusion of RCTs that compared a surgical procedure with conservative management. This mainly has implications for oncologic RCTs, as often different radiation and medical regimens are compared instead of a surgical procedure.[14] Lastly, only trial characteristics were comparable, which may limit our findings.

Future studies on the conduction of neurosurgical RCTs could study subspecialty specific trial characteristics even more profoundly and their influence on trial quality and findings. Also, investigating trials comparing a novel neurosurgical procedure to current standard of practice in a similar fashion to this study may give insightful information on how to better interpret their results. Finally, evaluation of neurosurgical RCTs could be aided by the introduction of a trial registry that is specific to neurosurgery and takes into account the unique challenges of a neurosurgical RCT.

Implication for future neurosurgical RCTs

The findings of this study regarding trial registry, patient accrual, trial completion, publication, and alteration of outcome measures provide suggestions for improvement of future neurosurgical RCTs. Neurosurgical RCTs should seek to answer questions that live among the neurosurgical community and are answerable by an RCT. This requires true equipoise, the availability of patients, and sufficient funding among other things. Other trial designs, such as a prospective observational study,

should be considered if they are more suitable to answer unresolved controversies in neurosurgery.[12]

Most journals nowadays require an RCT to be registered, disclose their funding sources, and publish a protocol to increase transparency. The protocol should ideally be published in a neurosurgical journal to provide a neurosurgical readership the possibility to suggest alterations to the trial design to improve trial quality and make the potential findings as relevant as possible. Alterations to outcome measures should always be disclosed to readers together with a reason for this alteration. Investigators should be realistic about in- and exclusion criteria to meet the estimated of number of patients to be included and should optimize the inclusion process. Similar to our results another study found trial discontinuation to be common in neurosurgical trials in general, most commonly due to slow recruitment.[6] A pilot study to evaluate the patient inclusion process that also provides an estimate of the outcome measure may aid this.[11] One study also found that telephone reminders to non-responders, opt-out procedures, and financial incentives may help patient inclusion.[21]

Although conducting a neurosurgical RCT may be considered burdensome, they should in the end provide answers of the highest possible quality that are relevant to the neurosurgical community. A well designed and conducted trial could make sure that the effort and funding put in do not go to waste. Again, all of this may be aided by the introduction of a trial registry that is specific to neurosurgery.

Conclusion

RCTs comparing surgical to conservative treatment remain rare in neurosurgery. Most RCTs identify a benefit for surgical treatment. However, outcome measurements change frequently and anticipated accrual of patient often differs from the number of included patients. Trial registration is still only done in half of RCTs and funding sources are not always reported. Nonetheless, these are not factors that influence a surgical benefit over conservative treatment in neurosurgical RCTs. Lastly, trial termination is not uncommon, with the most common reason being slow recruitment. Successfulness of future neurosurgical RCTs could be improved by trial registration prior to patient inclusion and pilot studies.

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Table 4.6: Search syntax

PubMed search: 1-2017	*(((((((neurosurg*[tw] OR cranial surg*[tw] OR spine surg*[tw] OR spinal surg*[tw] OR Temporal Lobectom*[tw] OR cortectom*[tw] OR "Brain Tissue Transplantation"[tw] OR "Cerebral Decortication"[tw] OR Hemispherectom*[tw] OR Cerebrospinal Fluid Shunt*[tw] OR Ventriculoperitoneal Shunt*[tw] OR CSF Shunt*[tw] OR VP Shunt*[tw] OR "Trephining"[tw] OR "Parasympathectomy"[tw] OR "Sympathectomy"[tw] OR neurectom*[tw] OR spinal fusion[tw] OR disc fusion[tw] OR ACDF[tw] OR spinal decompression[tw] OR "Microvascular Decompression Surgery"[tw] OR "Nerve Transfer"[tw] OR "Split-Brain Procedure"[tw] OR "Neuronavigation"[tw] OR "Radiosurgery"[tw] OR (SRS[tw] NOT sexual[tw]) OR gamma knife[tw] OR cyber knife[tw] OR stereotactic radiotherapy[tw] OR deep brain stimulation[tw] OR (DBS[tw] NOT double bare metal stent[tw]) OR neurostimulation[tw] OR neurostimulator[tw] OR spinal cord stimulator*[tw] OR spinal cord stimulation[tw] OR "Diskectomy"[tw] OR disc replacement[tw] OR spinal decompression[tw] OR spinal cord decompression[tw] OR Ventriculostom*[tw] OR Craniotom*[tw] OR cranioplast*[tw] OR Decompressive Craniectom*[tw] OR Corpus callosotomy[tw] OR Vagotom*[tw] OR Ganglionectom*[tw] OR Axotom*[tw] OR Cordotom*[tw] OR Ganglionectom*[tw] OR Rhizotom*[tw] OR Vagotom*[tw] OR Foraminotom*[tw] OR Hypophysectom*[tw] OR Laminectom*[tw] OR laminotom*[tw] OR Laminoplast*[tw] OR Neuroendoscop*[tw] OR endonasal[tw] OR Pallidotom*[tw] OR thalamotom*[tw] OR cortical resection*[tw] OR Psychosurg*[tw] OR microvascular decompression surgery[tw] OR Radiosurg*[tw] OR Diskectom*[tw] OR Discectom*[tw] OR cranial vault resconstruction[tw] OR cranial vault remodeling[tw] OR craniosynostosis surgery[tw] OR auditory brainstem implant[tw] OR transphenoidal surger*[tw] OR cerebral stent[tw] OR cerebral stents[tw] OR cerebral stenting[tw] OR carotid stent[tw] OR carotid stents[tw] OR carotid stenting[tw] OR carotid endarterectom*[tw] OR (CEA[tw] NOT carcinoembryonic antigen[tw]) OR (angioplasty[tw] NOT (cardiac[tw] OR coronary[tw])) OR aneurysm coiling[tw] OR aneurysm clipping[tw] OR neurosurgical clipping[tw] OR endovascular coiling[tw] OR cerebral bypass[tw] OR cranial bypass[tw] OR middle cerebral artery bypass[tw] OR ((embolization[tw] OR resection[tw]) AND (AVM[tw] OR arteriovenous malformation[tw])) OR ((resection[tw] OR resect[tw] OR debulk*[tw]) AND (brain[tw] OR cranial[tw] OR intracranial[tw] OR cerebral[tw] OR spinal[tw] OR CNS[tw] OR glioma[tw] OR glioblastoma[tw] OR meningioma[tw] OR astrocytoma[tw] OR GBM[tw] OR neuroma[tw] OR pituitary tumor*[tw] OR lymphoma[tw] OR brain tumor[tw] OR brain metastasis[tw] OR brain metastases[tw])) OR "Neurosurgery"[Mesh] OR "Neurosurgical Procedures"[Mesh] OR "Spine/surgery"[mesh] OR "Spinal Diseases/surgery"[mesh] OR "Brain/surgery"[mesh] OR "Brain Diseases/surgery"[mesh] OR "Central Nervous System/surgery"[mesh] OR "Central Nervous System Diseases/surgery"[mesh] OR "Nervous System/surgery"[mesh] OR "Nervous System Diseases/surgery"[mesh])))) AND ((randomized controlled trial[tw] OR randomized controlled study[tw] OR randomly assigned[tw] OR randomized trial[tw] OR randomized, double-blind, placebo-controlled trial[tw] OR randomized, double blind, controlled trial[tw] OR randomized, double blind[tw] OR randomized trial[tw] OR prospective, double blind[tw] OR controlled clinical trial[tw] OR randomized clinical trial[tw] OR double blind[tw] OR prospective clinical trial[tw] OR randomised controlled trial[tw] OR randomised controlled study[tw] OR randomised trial[tw] OR randomised, double-blind, placebo-controlled trial[tw] OR randomised, double blind, controlled trial[tw] OR randomised, double blind[tw] OR randomised trial[tw] OR randomised clinical trial[tw] OR ("Randomized controlled trial"[publication type])))*
Embase search: 1-2017	(neurosurg* or cranial surg* or spine surg* or spinal surg* or Temporal Lobectom* or cortectom* or "Brain Tissue Transplantation" or "Cerebral Decortication" or Hemispherectom* or Cerebrospinal Fluid Shunt* or Ventriculoperitoneal Shunt* or CSF Shunt* or VP Shunt* or "Trephining" or "Parasympathectomy" or "Sympathectomy" or neurectom* or spinal fusion or disc fusion or ACDF or spinal decompression or "Microvascular Decompression Surgery." or "Nerve Transfer" or "Split-Brain Procedure" or "Neuronavigation" or "Radiosurgery" or (SRS not sexual) or gamma knife or cyber knife or stereotactic radiotherapy or deep brain stimulation or (DBS not double bare metal stent) or neurostimulation or neurostimulator or spinal cord stimulator* or spinal cord stimulation or "Diskectomy" or disc replacement or spinal decompression or spinal cord decompression or Ventriculostom* or Craniotom* or cranioplast* or Decompressive Craniectom* or Corpus callosotomy or Vagotom* or Ganglionectom* or Axotom* or Cordotom* or Ganglionectom* or Rhizotom* or Vagotom* or Foraminotom* or Hypophysectom* or Laminectom* or laminotom* or Laminoplast* or Neuroendoscop* or endonasal or Pallidotom* or thalamotom* or cortical resection* or Psychosurg* or microvascular decompression surgery or Radiosurg* or Diskectom* or Discectom* or cranial vault resconstruction or cranial vault remodeling or craniosynostosis surgery or auditory brainstem implant or transphenoidal surger* or cerebral stent or cerebral stents or cerebral stenting or carotid stent or carotid stents or carotid stenting or carotid endarterectom* or (CEA not carcinoembryonic antigen) or (angioplasty not (cardiac or coronary)) or aneurysm coiling or aneurysm clipping or neurosurgical clipping or endovascular coiling or cerebral bypass or cranial bypass or middle cerebral artery bypass or ((embolization or resection) and (AVM or arteriovenous malformation)) or ((resection or resect or debulk*) and (brain or cranial or intracranial or cerebral or spinal or CNS or glioma or glioblastoma or meningioma or astrocytoma or GBM or neuroma or pituitary tumor* or lymphoma or brain tumor or brain metastasis or brain metastases))).tw. or (neurosurgery/ or auditory brain stem implantation/ or neuroendoscopy/ or neuronavigation/ or exp skull surgery/ or exp spinal cord surgery/ or exp sympathectomy/ or exp vagotomy/ or exp ventriculostomy/ or exp spine/su or exp spine disease/su or exp brain/su or exp brain disease/su or exp central nervous system/su or exp central nervous system disease/su or neurologic disease/su) AND ((randomized controlled trial or randomized controlled study or randomized trial or randomized, double-blind, placebo-controlled trial or randomized, double blind, controlled trial or randomized, double blind or randomized trial or randomized clinical trial or double blind or randomly assigned or prospective, double blind or controlled clinical trial or prospective clinical trial or randomised controlled trial or randomised controlled study or randomised trial or randomised, double-blind, placebo-controlled trial or randomised, double blind, controlled trial or randomised, double blind or randomised trial or randomised clinical trial).tw)