Pragmatism in Pediatric Neurosurgery: More Than a Pipe Dream? A Systematic Literature Review and Analysis

Charlotte C. Kik and Jochem K.H. Spoor

■ BACKGROUND: **Classic randomized controlled trials (RCTs) form the cornerstone for medical guidelines and protocols. However, in neurosurgery, RCTs are not always applicable to everyday clinical practice. Pragmatic controlled trials aim to incorporate real-life data with the preservation of the methodologic quality. This study is a systematic literature review of all pediatric neurosurgical RCTs published between 2000 and 2020 and an analysis of their pragmatism.**

■ METHODS: **An electronic database search was performed in PubMed, EMBASE, and the Cochrane Library to identify all relevant trials. Pragmatism was evaluated retrospectively on 9 domains: eligibility, recruitment, setting, organization, flexibility (delivery and adherence), follow-up, primary outcome, and primary analysis.**

■ RESULTS: **Of the 1862 studies included, 15 met the inclusion criteria. On average, studies scored between equally pragmatic/explanatory and rather pragmatic (M = 3.59, standard deviation [SD] = 0.56). Lowest ratings were seen for setting (M = 2.80, SD = 1.66) and eligibility (M = 3.20, SD = 1.66). Highest scores of pragmatism were given to analysis (M = 4.67, SD = 0.82) and intervention organization (M = 4.60, SD = 1.06). There was no significant difference between studies based on number of patients included, main subject, or publication year.**

■ CONCLUSIONS: **Pediatric neurosurgical RCTs scored reasonably well on overall pragmatism. In the future, there will be a greater need for pragmatic controlled trials in pediatric neurosurgery to bridge the divide between real-life data and reliable methodological quality. There is an opportunity to develop further applications of pragmatism tailored to surgical interventions.**

INTRODUCTION

All patients are created equal, but are some created more equal than others? Contrary to the clear markers set in clinical outlines, patients rarely fit these neatly defined boxes. Similarly, health care professionals often diverge from guidelines to offer personalized treatment for individual cases. Everyday clinical practice is a combination of experience, training, and insights drawn from (new) research. Classical randomized controlled trials (RCTs) form the cornerstone for our guidelines and protocols, but do they reflect real-life clinical practice as well as more pragmatically designed studies do?

The RCT is considered to provide one of the highest forms of medical evidence. On the basis of the principle of equipoise, an RCT study allows for the randomization of patients while preserving ethical parity.[1,2] In neurosurgery, however, similarly to other surgical specialties, this equilibrium is often impractical or even impossible to maintain between patients.[3-6] For example, standardization of surgical techniques and skills is challenging to establish. Most importantly, clinical decision making is primarily based on experience and expertise instead of a rigid framework set by protocols.[7]

Pediatric neurosurgical RCTs, in particular, have encountered criticism on the everyday practicality of their design.[8] As defined by the U.S. Food and Drug Administration, real-world evidence is derived from both the data source and the degree of pragmatism.[9] Driven by "real-world data," pragmatic RCTs (PCTs) present an alternative solution. PCTs, contrary to explanatory

Key words
- Neurosurgery
- Pragmatic clinical trial
- Randomized controlled trial

Abbreviations and Acronyms
ANOVA: Analysis of variance
PCT: Pragmatic controlled trial
PRECIS: Pragmatic-Explanatory Continuum Indicator Summary
RCT: Randomized controlled trial

Department of Neurosurgery, Erasmus Medical Center, Rotterdam, The Netherlands

To whom correspondence should be addressed: Jochem K. H. Spoor, M.D. [E-mail: j.spoor@erasmusmc.nl]

The authors contributed equally to the study.

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RCTs, test hypotheses on whether the intervention causes an outcome of interest in real-life circumstances.[10] PCTs also maintain the prognostic balance established by RCTs while permitting other aspects to proceed as routine. Whereas explanatory RCTs predominantly aspire to ensure their internal validity, PCTs aim to maximize their external validity to improve generalizability.

In theory, PCTs seem suitable to bridge the gap between RCT and clinic. However, what requirements do PCTs have to fulfill to be considered "pragmatic"? Real-world data-driven research has gained tremendous popularity in recent years, and many new studies are self-characterized as practical. In general, PCTs must consist of at least 2 fundamental components.[10] On the one hand, the study's layout should be representative of everyday clinical practice. On the other, the results must also be applicable across a multitude of different settings.

To further quantify and standardize the degree of pragmatism, the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)-2 tool was created.[11] It allows for prospective and retrospective assessment of the degree of pragmatism on 9 domains: eligibility, recruitment, setting, organization, flexibility (delivery and adherence), follow-up, primary outcome, and primary analysis. As a result, a visualization of an RCT's level of pragmatism on the pragmatic to explanatory continuum can be established. This study aims to retrospectively evaluate the pragmatism of pediatric neurosurgical RCTs between 2000 and 2020 using the PRECIS-2 tool.

MATERIAL AND METHODS

Literature Search

This review was conducted in concordance with the PRISMA guidelines for transparent reporting of systematic reviews.[12] Studies containing neurosurgical procedures for the pediatric and fetal population published between January 1, 2000 and December 31, 2020, were screened independently by 2 investigators (C. C. K., J. K. H. S). An electronic database search was performed in both PubMed, EMBASE, and Cochrane Library using the following key words: neurosurgery, neurosurgical procedures, discectomy, craniotomy, fetoscopy, ventriculoperitoneal shunt, external ventricular drain, epilepsy, vagal nerve stimulation, cerebral infarction/hemorrhage, intracranial aneurysm, carotid artery injuries, brain neoplasms, spinal dysraphism, laminectomy using the Boolean operator AND for the population. Additional publications were identified through citation chaining, database, and journal research.

Study Selection and Data Extraction

Both investigators reviewed titles and abstracts for relevance using the online review tool Rayyan (http://rayyan.qcri.org).[13] RCTs with neurosurgical interventions aimed at the pediatric or fetal population were included. If consensus on the included full-text studies could not be achieved, a third independent investigator was consulted. Investigators extracted the following data: study design, year of publication, study location and period, study subject, type of intervention, gender distribution, and mean or median age.

Assessment of Pragmatism

The PRECIS-2 tool was used to evaluate each study on its level of pragmatism. The PRECIS-2 tool evaluates pragmatism on 9 domains: eligibility, recruitment, setting, organization, flexibility (delivery and adherence), follow-up, and primary outcome.[11] Scores are based on a 5-point Likert scale, ranging from very explanatory (1) to very pragmatic (5). The flexibility of adherence to the intervention was not applicable for surgical trials, as there is no compliance issue after consent has been given. Consequently, under these circumstances, no score was given to this subdomain.

Data Synthesis

Overall pragmatism was calculated per study as the average score from all 9 or, in surgical trials, 8 subdomains. In addition, 3 subgroups were created on the basis of publication year, number of patients included, and main subject. For group division based on publication year, studies published between 2000 and 2005, 2006 and 2010, 2011 and 2015, and 2016 and 2020 were grouped. Other groups based on the number of patients included divided studies with $\leq$10, 10–50, 51–100, and >100 patients. Finally, studies were organized by main subject: hydrocephalus, spinal dysraphism or tethering, epilepsy, or traumatic brain injury.

Statistical Analysis

Summary estimates were calculated as the mean PRECIS-2 score $\pm$standard deviation. A 1-way analysis of variance (ANOVA) was conducted to determine whether there was a significant difference in PRECIS-2 scores for groups based on publication year, main study subject, or number of patients included. If the assumption of homogeneity of variance could not be met, analysis was converted to the Welch ANOVA. Post-hoc analysis, in case of significant difference between groups, was performed via a Mann-Whitney U test. Outliers were evaluated by visual inspection of boxplots. The Shapiro-Wilk test assessed normal data distribution. Homogeneity of variance was determined by the Levene test of equality of variances. All analyses were performed using SPSS 26.0 (IBM CORP, released 2019, IBMS SPSS Statistics for Windows, version 26.0, IBM Corp., Armonk, New York, USA).

RESULTS

Study Selection and Inclusion

The electronic database search of PubMed, EMBASE, the Cochrane Library, clinicaltrial.gov, and clinicaltrialsregister.eu yielded 1862 studies, of which 14 were identified as duplicates. Of the 1848 studies screened for abstract and title, 57 articles were found eligible for full-text assessment. Subsequently, 42 articles were excluded for various reasons including not reporting the population of interest ($n = 23$), the wrong study design ($n = 12$), or publication type ($n = 1$) and additional duplicates

Table 1. Study Characteristics and Mean Pragmatic-Explanatory Continuum Indicator Summary–2 Scores per Study

		Study Period					Gender		Age (In Years)		PRECIS-2
Authors	Location	From	Until	Subject	Intervention	Number of Patients	Male	Female	Mean	Median	Mean Score
Navaei et al.[23]	Tehran, Iran	2012	2015	Hydrocephalus	VPS versus ETV & ECPC	49	32	17	3.74	NA	3.63
Aranha et al[15]	New Dehli, India	2015	2017	Hydrocephalus	VPS versus ETV	52	31	21	NA	NA	4
Kulkarni et al.[21]	International multicenter	2005	2013	Hydrocephalus	VPS versus ETV	52	NA	NA	NA	1.62	3.5
Dwivedi et al.[16]	New Dehli, India	2010	2015	Epilepsy	Epilepsy surgery versus pharmaceutical control	116	44	72	9.8	NA	4.13
Tuite et al.	Baltimore, USA	2009	2012	Spinal tethered cord syndrome	Detethering & Xiao procedure versus detethering	20	NA	NA	NA	NA	3.25
Steinbok et al.[27]	Vancouver, Canada	NA	NA	Spinal tethered cord syndrome	Filum section versus pharmaceutical control	21	5	16	9.3	NA	2.88
Oliveria et al.[24]	São Paulo, Brazil	2010	2012	Hydrocephalus	Retrograde ventricle-sinus shunt versus VPS	9	6	3	0.42	NA	3.38
Goyal et al.[18]	Lucknow, India	2010	2013	Hydrocephalus	VPS versus ETV	48	34	14	4.6	NA	4.38
Adzick et al.[14]	Multicenter, USA	2003	2010	Spinal dysraphism	Prenatal versus postnatal myelomeningocele repair	158	72	86	<0	NA	2.25
Malheiros et al.[22]	Belo Horizonte, Brazil	2006	2008	Hydrocephalus	ECPC versus VPS	17	4	13	0.32	NA	4.13
Khan et al.[20]	Chandigarh, India	NA	NA	Hydrocephalus	Antisiphon VPS versus nonantisiphon VPS	40	29	11	0.29	NA	4
Whitelaw et al.[28]	International multicenter	2003	2006	Hydrocephalus	DRIFT versus cerebrospinal tap	70	47	23	0.05	NA	3.38
Kestle et al.[19]	Multicenter, USA	1996	1999	Hydrocephalus	Endoscopic versus nonendoscopic VPS	393	216	177	NA	0.25	4
Taylor et al.[26]	Melbourne, Australia	1991	1998	Traumatic brain injury	Early decompression versus medical management	27	NA	NA	10.1*	NA	3.75
Erkan et al.[17]	Istanbul, Turkey	1992	1998	Spinal tethered cord syndrome	Detethering & syrinx decompression versus detethering	30	NA	NA	6.2	NA	3.25

VPS, ventriculoperitoneal shunt; ETV, endoscopic third ventriculostomy; ECPC, endoscopic choroid plexus cauterization; NA, not available; DRIFT, drainage, irrigation and fibrinolytic therapy.

Table 2. Overall PRECIS-2 Score and Subgroup Analysis

		PRECIS-2 Score			
	Number	Mean	Standard Deviation	Min	Max
All studies	15	3.60	0.56	2.25	4.38
Subgroup—publication year					
2000–2005	3	3.67	0.38	3.25	4.00
2006–2010	3	3.83	0.40	3.38	4.13
2011–2015	3	3.33	1.06	2.25	4.38
2016–2020	6	3.56	0.47	2.88	4.13
Subgroup—number of included patients					
<10	1	3.38	0.00	3.38	3.38
11–50	8	3.66	0.51	2.88	4.38
51–100	3	3.63	0.33	3.38	4.00
>100	3	3.46	1.05	2.25	4.13
Subgroup—main subject					
Hydrocephalus	9	3.58	0.58	2.25	4.13
Epilepsy	1	4.13	0.00	4.13	4.13
Spinal dysraphism & tethering	4	3.44	0.65	2.88	4.38
Traumatic brain injury	1	3.75	0.00	3.75	3.75

($n = 6$). Finally, 15 studies were included for the assessment of pragmatism.[14-28]

Study Characteristics

Study and patient characteristics are summarized in Table 1. All of the 15 included studies consisted of RCTs with children as their only population of interest. Study periods ranged from 1992 until 2015. Studies mainly reported on interventions aimed at hydrocephalus ($n = 9$), spinal dysraphism or tethering ($n = 4$), epilepsy ($n = 1$), and traumatic brain injury ($n = 1$). In total, 520 male and 453 female patients were included. The mean age ranged from <0 years to 10.1 years.

Evaluation of Pragmatism

The 15 included studies were each individually scored on all 9 subdomains of the PRECIS-2 score. On average, studies scored between equally pragmatic/explanatory and rather pragmatic ($M = 3.59$, $SD = 0.56$). Lowest ratings were seen for setting ($M = 2.80$, $SD = 1.66$) and eligibility ($M = 3.20$, $SD = 1.66$). Highest scores of pragmatism were given to analysis ($M = 4.67$, $SD = 0.82$) and intervention organization ($M = 4.60$, $SD = 1.06$). No study received scores for the subdomain "flexibility to the adherence of the experimental intervention" since all studies included surgical interventions.

Subgroup Analysis

A 1-way ANOVA was conducted to determine whether pragmatism scores were different for groups based on publication year, number of patients included, and main subject (Table 2). There were no outliers, as assessed by boxplot; data were normally distributed for each group, as assessed by Shapiro-Wilk test ($P > 0.05$); and variances were homogeneous, as assessed by the Levene test of variances ($P = 0.060$, $P = 0.772$, $P = 0.778$).

Pragmatism scores did not significantly increase between group years $F(3, 11) = 0.368$, $P = 0.778$; 2000–2005 ($n = 3$) ($M = 3.67$, $SD = 0.38$), 2006–2010 ($n = 3$) ($M = 3.83$, $SD = 0.40$), 2011–2015 ($n = 3$) ($M = 3.33$, $SD = 1.06$), 2016–2020 ($n = 6$) ($M = 3.56$, $SD = 0.47$). Pragmatism scores were higher for studies with epilepsy ($n = 1$) ($M = 4.13$, $SD = 0.0$) and trauma ($n = 1$) ($M = 3.75$, $SD = 0.00$) as main subject as compared with hydrocephalus ($n = 9$) ($M = 3.58$, $SD = 0.58$) and spinal dysraphism or tethering ($n = 4$) ($M = 3.43$, $SD = 0.64$), but this difference was not statistically significant $F(3, 11) = 0.376$, $P = 0.772$. Similarly, studies that included larger groups of patients did not score significantly higher on pragmatism $F(3, 11) = 0.119$, $P = 0.947$; ≤10 patients ($n = 1$) ($M = 3.38$, $SD = 0.00$), 11 until 50 patients ($n = 8$) ($M = 3.66$, SD 0.51), 51 until 100 patients ($n = 3$) ($M = 3.63$, SD 0.33), >100 patients ($n = 3$) ($M = 3.46$, SD 1.05).

DISCUSSION

In summary, pediatric neurosurgical RCTs scored reasonably well on overall pragmatism. Strong pragmatic recruitment can be attributed to the inclusion of patients through regular appointments or clinic. No studies were seen that recruited patients on the basis of, for instance, targeted invitation letters, newspaper advertisements, or other incentive routes. Although this review included 2 multicenter studies, RCTs mainly took place in a single or academic center, contributing to lower scores on the subdomain for setting. Despite the fact that the implementation of real-life data has become of greater importance, no increase in pragmatism was seen throughout the years. Similarly, more extensive studies that included larger groups of patients or studies that were part of a more prominent main subject did not increase pragmatism.

The PRECIS-2 tool is the only application currently available to evaluate pragmatism in RCTs. Whereas it is valuable for its prospective and retrospective applicability, it also bears limitations. Although the tool can be used on any RCT, not all subdomains are suited to evaluate surgical interventions. For instance, treatment adherence is not relevant after consent for treatment has been given. In addition, recruitment for pediatric surgical trials rarely takes place outside clinics. Due to ethical restraints associated with the pediatric population, there is little concern for trials offering incentives beyond usual care.

Surgical RCTs are challenging to perform, especially in the pediatric population. Beyond the small sample sizes and ethical limitations, strict inclusion criteria can reduce applicability in clinical practice. For instance, the MOMS trial, which evaluated prenatal versus postnatal repair of myelomeningocele, excluded mothers with a body mass index of 35 or more. In an age where obesity is on the rise, this study severely limited the population that may have benefitted from this intervention. The rationale

behind such constraints, such as concern for increased maternal complications and preterm delivery, are in most cases credible. However, it is debatable whether studies tailoring to a smaller group benefit the population as a whole.

Furthermore, uniformity in surgical techniques does not allow for peroperative changes or differences in skill between surgeons. Surgery cannot be performed without allowing for interpretation and adaption based on anatomic variety. This flexibility, although necessary, increases the risk of bias between included patients. Similarly, surgical proficiency through experience imposes the risk of bias between specialists. Despite the success of some blinding techniques for surgical interventions, this difference in expertise is a complex limitation in multicenter settings.

Compared with the rigid inclusion criteria illustrated earlier, primary endpoints can be equally stringent when translating to the daily clinic.[14,23] The skull's drive to grow is largely formed by the growth of the brain. This stimulus can be reduced by shunt placement. Treatment of syndromic craniosynostosis with an endoscopic third ventriculostomy (ETV) often results in the insertion of a shunt months later. This shunt placement, in a trial with a rigid endpoint, could be considered a failure of the ETV. However, a prolonged period between initial intervention and the implementation of a shunt could also be seen as favorable since it allows for vault expansion. It raises the question of what defines a successful endpoint in the eyes of the patient and whether current RCTs adequately reflect their preferences?

In the future, there will be a greater need for PCTs in pediatric neurosurgery to bridge the divide between real-life data and reliable methodologic quality. There is an opportunity to develop further applications tailored to surgical interventions. In this way, researchers will be able to evaluate the pragmatism of their study and assess the importance of the primary outcome in an early phase. While mainly contributing to a more realistic implementation of RCTs in daily practice, PCTs can improve the incorporation of patients' primary goals of care. Regardless of its inventions, the main goal of an RCT is to contribute to a better understanding of what defines the best clinical care. With the need for more multicenter trials, PCTs can further guide the integration between trial and clinic.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Charlotte C. Kik: Conceptualization, Methodology, Software, Investigation, Data curation, Writing — original draft. **Jochem K.H. Spoor:** Conceptualization, Software, Investigation, Data curation, Writing — original draft, Supervision.

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