No child left behind

Akash P Kansagra

An explosion of clinical trials over the last decade has transformed neurointervention from its awkward, adolescent phase into a mature, evidence-based subspecialty. The show-and-tell slideshows of that earlier era have given way to talks that are an alphabet soup of trial acronyms. Much work remains, but these undeniable advances in knowledge have paved the way for real and meaningful progress in the care of adults with neurovascular disease.

Unfortunately, pediatric patients have been left behind. There is a profound dearth of clinical evidence guiding the appropriate use of neurointerventional therapies in children. The challenges of generating clinical evidence in children are not unique to our field,[1] but the contrast between pediatric care and high-quality, evidence-based, and potentially lifesaving care that is readily available to adults is particularly striking in neurointervention. As we contemplate the next generation of clinical trials to improve the care of patients with neurological disease, it is worth drawing attention to three diseases for which reliable pediatric evidence is sorely needed.

THROMBECTOMY FOR ACUTE ISCHEMIC STROKE

Those accustomed to caring for adults with acute ischemic stroke (AIS) may be surprised to learn that AIS has an estimated incidence of 1.7 per 100 000 per year in children,[2] about the same as pediatric brain tumors. Even this incidence is thought to be an underestimate due to failures in diagnosing pediatric AIS. The impact of pediatric AIS is magnified by the greater potential loss of quality-adjusted life years in children. Thus, there is great need to understand how to use thrombectomy in children with AIS.

Unfortunately, one cannot glean this information from adult trials. The etiologies of pediatric AIS differ substantially from adults and include a far higher proportion of congenital heart disease, coagulation disorders, and non-atherosclerotic arteriopathies. Moreover, children with AIS have vastly different presentations from adults. Approximately 48% of children experiencing AIS present with seizure,[3] a symptom that is not featured in any adult thrombectomy trial. Children also often experience astounding delays in AIS diagnosis that would be unthinkable in adults, and the perfusion imaging selection utilized in adult trials of extended window thrombectomy may not be available or valid in children due to concerns about radiation exposure and different thresholds of abnormal perfusion.[4] Finally, there is likely considerable age-dependence in treatment effect, especially for the youngest of children in whom neuroplasticity and a capacity for functional adaption can confer some resilience to AIS-related disability.

Why should we not then simply rely on currently available pediatric thrombectomy data? The overwhelming majority of published data for pediatric thrombectomy is retrospective. Using retrospective data might be a reasonable concession if not for the fact that these data have been shown to be biased and incomplete. One recent consortium-led study employed robust data collection practices derived from an earlier prospective pediatric AIS trial and found that, compared with the wider pediatric literature, their cohort had less improvement in symptoms (median National Institutes of Health Stroke Scale (NIHSS) improvement of 3 vs 8) and was significantly less likely to omit clinical outcome measures that would be essential in any AIS trial.[5]

TREATMENT OF ARTERIOVENOUS MALFORMATIONS

Children represent a sizeable proportion of the overall population of patients in need of brain arteriovenous malformation (AVM) management. This skew toward young age ostensibly reflects the presence of these lesions in early life and screening programs in patients with syndromes known to predispose to AVM formation. Unlike in adults, brain AVMs are the most common cause of non-traumatic intracranial hemorrhage in children. Thus, pediatric considerations loom large in brain AVM practice.

Nowhere is this more apparent than during the selection of treatment modality. Modern brain AVM treatment may include any combination of microsurgery, radiosurgery, and endovascular embolization. In children, two of these therapies—radiosurgery and endovascular embolization—pose unique challenges due to the need for considerable exposure to ionizing radiation.

Several pieces of new evidence indicate that pediatric brain AVMs behave and respond to treatment differently compared with adults. Though brain AVMs have historically been considered congenital lesions, emerging reports describe formation of AVMs during childhood.[6] While the precise mechanisms of formation are not fully understood, it is important to recognize that AVMs in children may be dynamic. Along the same lines, three recent studies have reported a 10–15% rate of pediatric brain AVM recurrence after treatment, even after angiographically confirmed obliteration.[7–9] These studies further highlight the differing risk of AVM recurrence based on treatment modality, with radiosurgery demonstrating the lowest risk of recurrence and endovascular embolization with curative intent demonstrating the highest risk.[7 8] These uniquely pediatric considerations are not reflected in the ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial, which did not include any children, or the forthcoming TOBAS) (Treatment of Brain AVMs Study) trial, which to date has enrolled few children.

INTRA-ARTERIAL CHEMOTHERAPY FOR RETINOBLASTOMA

The primary goal of treatment in children with intraocular retinoblastoma is tumor control, but globe salvage is an important secondary goal. While several therapies exist to treat intraocular retinoblastoma—chemotherapy, cryosurgery, laser ablation, external beam radiation, and surgical enucleation chief among them[10]—there has been particular interest in intra-arterial chemotherapy (IAC) as a means to achieve globe salvage.[11]

In some patients, IAC is the only viable alternative to the far more drastic option of enucleation. IAC works by delivering a high local concentration of chemotherapy at the tumor site while minimizing systemic effects that could otherwise limit the dose of drug that can be administered. Early results from a handful of facilities have been promising, demonstrating the ability to salvage most eyes with low-grade retinoblastoma, many eyes with high-grade disease, and even a majority of eyes that had already received intravenous chemotherapy or showed evidence of subretinal or vitreous tumor seeding.[12 13]

Correspondence to Dr Akash P Kansagra, Santa Clara Valley Medical Center, Santa Clara, California, USA; apkansagra@gmail.com

Despite these encouraging data, IAC is not universally available, even at some hospitals that routinely treat children with retinoblastoma. Where IAC is offered, there may be significant variations in drug dose and regimen, with different centers commonly offering site-specific combinations of melphalan, topotecan, and carboplatin. The incidence of treatment failure, chemotherapy-related adverse effects, and procedural complications is also not rigorously known, especially outside of a few highly experienced centers. These are extremely important considerations that warrant detailed study before specific treatment regimens can be recommended.

RETHINKING OUR APPROACH

It may seem odd to discuss ischemic stroke, hemorrhagic stroke, and cancer in the same breath. But beneath these labels, the research challenges—and potentially the solutions—are largely the same.

For each condition, conventional randomized clinical trials are no longer feasible. For one, loss of clinical equipoise poses pragmatic and ethical barriers to unbiased enrollment. Can we really imagine withholding thrombectomy in a 17-year-old with large vessel occlusion, surgery in an adolescent with a low-grade but recently ruptured AVM, or IAC in a toddler otherwise destined for enucleation? Moreover, the inability to scale down the cost and time commitment of conventional trials to account for anticipated low per-site enrollment will lead to unacceptably high per-subject cost and effort. These barriers have repeatedly frustrated efforts to obtain high quality, prospective data for neurointerventional therapies in children.

The solution may therefore need to be unconventional. Rather than evaluating each disease on its own, can we study them together? Novel clinical trial designs, including so-called super umbrella studies, already touch on this idea by evaluating one or more treatments across several related diseases.[14] Perhaps we can adapt this concept to develop a national trial that can take advantage of economies of scale, offering infrastructure for study monitoring, data collection and governance, adverse event reporting, and statistical analysis that is shared across all three diseases. Study costs can be further mitigated by employing digital health tools to collect some data directly from patients, as is done in virtual clinical trials,[15] reducing the burden of data collection at each site. Our neurointerventional community has demonstrated enormous capacity for innovation and has already improved the care of patients with these conditions. It is time to harness this creativity to improve the state of research in pediatric patients with these three diseases, overcoming the barriers that have excluded children from the most important advances in our field.

X Akash P Kansagra @AkashKansagra

Contributors I am the sole author.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Kansagra AP. *J NeuroIntervent Surg* 2024;**16**:535–536.

Accepted 24 April 2024

J NeuroIntervent Surg 2024;**16**:535–536. doi:10.1136/jnis-2024-021907

ORCID iD

Akash P Kansagra http://orcid.org/0000-0002-9201-4551

REFERENCES

1 Furth SL. Trials and tribulations - the challenges of clinical trials in children. *NEJM Evid* 2023;2.
2 deVeber GA, Kirton A, Booth FA, *et al*. Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian pediatric ischemic stroke registry. *Pediatr Neurol* 2017;69:58–70.
3 deVeber G, Roach ES, Riela AR, *et al*. Stroke in children: recognition, treatment, and future directions. *Semin Pediatr Neurol* 2000;7:309–17.
4 Lee S, Heit JJ, Albers GW, *et al*. Neuroimaging selection for thrombectomy in pediatric stroke: a single-center experience. *J Neurointerv Surg* 2019;11:940–6.
5 Barry M, Barry D, Kansagra AP, *et al*. Higher-quality data collection is critical to establish the safety and efficacy of pediatric mechanical thrombectomy. *Stroke* 2021;52:1213–21.
6 Santos R, Aguilar-Salinas P, Entwistle JJ, *et al*. De novo arteriovenous malformation in a pediatric patient case report and review of the literature. *World Neurosurg* 2018;111:341–5.
7 Hak J-F, Boulouis G, Kerleroux B, *et al*. Pediatric brain arteriovenous malformation recurrence: a cohort study, systematic review and meta-analysis. *J Neurointerv Surg* 2022;14:611–7.
8 Lauzier DC, Vellimana AK, Chatterjee AR, *et al*. Return of the lesion: a meta-analysis of 1134 angiographically cured pediatric arteriovenous malformations. *J Neurosurg Pediatr* 2021;28:677–84.
9 Copelan A, Drocton G, Caton MT, *et al*. Brain arteriovenous malformation recurrence after apparent microsurgical cure: increased risk in children who present with arteriovenous malformation rupture. *Stroke* 2020;51:2990–6.
10 Schaiquevich P, Francis JH, Cancela MB, *et al*. Treatment of retinoblastoma: what is the latest and what is the future?. *Front Oncol* 2022;12.
11 Kocharian G, Gobin YP, Kharas N, *et al*. Advancements in super-selective catheterization and drug selection for intra-arterial chemotherapy for retinoblastoma: a 15-year evolution. *J Neurointerv Surg* 2024;16:398–404.
12 Shields CL, Manjandavida FP, Lally SE, *et al*. Intra-arterial chemotherapy for retinoblastoma in 70 eyes: outcomes based on the international classification of retinoblastoma. *Ophthalmology* 2014;121:1453–60.
13 Ravindran K, Dalvin LA, Pulido JS, *et al*. Intra-arterial chemotherapy for retinoblastoma: an updated systematic review and meta-analysis. *J Neurointerv Surg* 2019;11:1266–72.
14 Ioannidis JPA, Khoury MJ. Evidence-based medicine and big genomic data. *Hum Mol Genet* 2018;27:R2–7.
15 Shore C, Khandekar E, Alper J, eds. In: Virtual clinical trials: challenges and opportunities. Proceedings of a workshop; Washington (DC), 2019