Complication Avoidance and Management Research

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Abbreviations

ARUBA	A Randomized trial of Unruptured Brain Arteriovenous malformations
COSS	Carotid Occlusion Surgery Study
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
DVT	Deep vein thrombosis
EC-IC	Extracranial-intracranial
EEG	Electroencephalography
ICG	Indocyanine green
ICH	Intracerebral hemorrhage
ISUIA	The International Study of Unruptured Intracranial Aneurysms
MEP	Motor-evoked potential
PE	Pulmonary embolism
PET	Positron emission tomography
SEP	Sensory evoked potentials
TIA	Transient ischemic attack
TPA	Tissue plasminogen activator
VTE	Venous thromboembolism

Introduction

Research into complication avoidance and management begins with a clear definition of what constitutes a complication. This proves to be surprisingly difficult. An example is interpretation of the results of the CREST trial [1] for carotid stenosis in comparing the periprocedural stroke and myocardial infarction (MI) risk between the two treatment modalities studied—carotid endarterectomy (CEA) and carotid artery stenting (CAS). The trial reported higher stroke risk with CAS (4.1 vs. 2.3%; $p = 0.01$), which led proponents of CEA to propose that CEA was the preferable procedure of the two for stroke prevention. However, proponents of CAS argued that the vast majority of strokes were minor and non-disabling (81%) and pointed to the increased risk of MI with CEA (1.1 vs. 2.3%; $p = 0.03$). Counterarguments were that stroke was more impactful than MI on quality of life measures, while again pro-CAS experts noted that cranial neuropathy and/or MI were important enough to be considered as major complications of CEA. This preceding brief discussion is illustrative of the conundrum of defining a complication: what constitutes a complication to one group may be an acceptable side effect to the other and vice versa. Indeed this difference may be more disparate from the perspective of the patient. For instance, temporal muscle atrophy following pterional craniotomy for a complex incidental unruptured middle cerebral artery aneurysm requiring innovative clip reconstruction with bypass may be considered a minor expected trade-off for a highly involved procedure by the surgeon, whereas for the index patient, this may prove to be so irksome that it impacts daily social interactions. The latter may well be considered a complication of surgery in the patient's eyes. Similarly, aneurysm recurrence following coiling which necessitates further angiography, radiation, anesthesia, and intracranial arterial catheterization with its attendant risks may be considered expected "aneurysm maintenance" by the surgeon but a complication by the patient.

The elusiveness in defining a complication is expertly discussed in a thought-provoking paper by Sokol and Wilson in 2008. Through a stepwise development, they propose defining a surgical complication as "any undesirable, unintended, and direct result of an operation affecting the patient, which would not have occurred had the operation gone as well as could reasonably be hoped." This implies an error of *commission*. We however believe that there is also a distinct category of adverse health outcomes that result from errors of *omission* (Table 8.1). For example, the inability to detect an aneurysm that ultimately presents with fatal rupture could be construed as a complication resulting from non-diagnosis. Therefore research into complication avoidance could be organized into the following categories/phases of patient care:

1. Screening for disease detection and patient selection for treatment
2. Perioperative morbidity
3. Follow-up

Table 8.1 Illustrative examples of the role of research in aspects of neurovascular disease management

Disease	Challenge	Type of complication	Research focus	Proposed study method
Intracranial aneurysm	Fatal rupture after detection where treatment was withheld per ISUIA criteria	Omission	Hemodyanamic and morphologic factors predicting rupture (beyond size)	Natural history studies, prospective disease registry, prospective observational cohort studies incorporating flow dyanamics at different time points
	Intraoperative rupture	Commission	Safer anesthetic and surgical technique in operating room and endovascular suite	Patient-specific simulation
	Incomplete coil occlusion of wide-necked aneurysm or residual after clip reconstruction	Omission	Novel devices for aneurysm occlusion	Prospective device registry with long-term follow-up
Arteriovenous malformation (AVM)	Debilitating seizures from withholding definitive microsurgery for grade 1 AVM per ARUBA	Omission	Better assessment of treatment risks	Characterizing AVM hemodynamics with novel imaging such as NOVA at different time points in natural history and treatment
Carotid stenosis	Stroke during stent	Commission	Enhanced distal protection devices	Healthy collaboration with industry for innovation in device development
	Recurrent stenosis after CEA from progressive atherosclerosis	Omission	Optimization of risk factor management	Community-based behavioral intervention care paths
	Progressive cognitive decline due to hypoperfusion from carotid occlusion and withholding bypass per COSS	Omission	Cognitive assessment at different time points, with and without intervention	Randomized protocol-based study incorporating robust and reproducible scales

Table 8.1 (continued)

Disease	Challenge	Type of complication	Research focus	Proposed study method
Acute stroke	Hemorrhage from TPA in a patient who also underwent mechanical thrombectomy	Commission	Optimizing outcomes of endovascular recanalization independent of TPA	High-quality multicenter prospective cohort design compared to simultaneously collected controls matched as best as possible (randomization impossible given TPA is a standard of care currently)
	Continued aphasia from dominant M2 occlusion	Omission	Demonstration of feasibility of endovascular intervention	Prospective randomized trial design of outcomes after M2 recanalization
ICH	Progressive hematoma expansion and perihematoma brain injury	Omission	Minimally invasive clot evacuation and drugs delivered locally or systematically	Rapid phase 1/2 trials of novel clot stabilizing/ dissolution agents

Each in turn can focus on errors of omission or commission. In this chapter, we shall consider some relevant examples and scenarios where research on complications can improve patient outcomes in neurovascular surgery (defined as any technique involved in treating neurovascular diseases).

Types of Research

Several methods exist to study the above components:

1. Case reports
2. Case series
3. Epidemiologic studies
4. Database analysis or registry studies
5. Prospective observational studies
6. Clinical trials (matched cohorts and randomized)
7. Simulation studies and modeling
8. Surgical procedural protocol standardization studies [2]

Prospective clinical trials typically progress through Phases I to IV with Phase III trials constituting the benchmark randomized controlled trials (RCT) (with blinding) [2]. Data proven in RCTs are most robust since data is gathered prospectively in comparison with a control group and with well-defined endpoints while accounting and controlling for variability and bias. It must be realized that these are

very expensive, time consuming, and involve vast resources at each stage. Clinical trials may examine screening, prevention, diagnosis, treatment, and quality of life. Behavioral interventional studies that introduce and modify operational procedures in the operating room and angiography suite hold great promise toward quality initiatives [3]. A limitation of clinical trials is they are best suited for homogenous diseases where equipoise is clearly established for two treatments. This is problematic in neurosurgery where diseases are often highly heterogenous and equipoise is often lacking or controversial.

Screening and Patient Selection

Efficient screening that detects asymptomatic/preclinical disease can potentially reduce "omission"-related complications. General screening of entire populations has the best chance of detecting asymptomatic disease but has not been well defined for cerebrovascular diseases. Targeted screening has a role but defining the target population is not straightforward. A growing body of literature on familial aneurysms has made it easier to justify familial screening.

Intracranial Aneurysm

For cerebral aneurysms, screening of persons with two or more first-degree relatives has demonstrated increased incidence of aneurysms [4], but the perception on cost-effectiveness or impact on outcomes has not been uniform [5–7]. Even in diseases such as polycystic kidney disease, screening is deemed to be of utility if performed selectively [8]. Once detected, there is the issue of selecting appropriate patients for treatment since benefits despite therapy-related morbidity should outweigh the risks. The ISUIA trial, in two parts, attempted to answer this question for aneurysms, but several significant study limitations preclude blanket recommendations—the study had inherent serious selection bias, overestimates the prevalence of aneurysms, about 1/3 of patients in the prospective second part (2003) switched to treatment arms and were excluded from follow-up, and includes cavernous carotid aneurysms [7, 9]. The trials do highlight the relative lower rupture risks for small aneurysms less than 7 mm (during 5 years of follow-up) for anterior circulation but lend no credence to aneurysm morphology or hemodynamics which has been shown to potentially influence rupture risk [10–13]. The latter are ripe areas for research into enabling better patient selection for treating unruptured aneurysms detected following screening (or as an incidental finding). Selection bias related to enrolling low-risk aneurysms undoubtedly influenced results. A number of studies since ISUIA have suggested a higher rupture risk for small aneurysms [14].

AVM

The management of unruptured AVMs is challenging because of their variable hemorrhage risk and highly diverse morphologies and brain locations. Attempts have been

made to characterize this risk by incorporating individual AVM-related factors [15]. There are however pertinent AVM factors that are still inconsistently characterized in AVM scores. Comprehensive hemodynamic characterization of an AVM including the venous component coupled with prospective collaborative database analysis is an exciting possibility toward consistent and accurate prediction of rupture risk [16]. Patient selection for treatment of brain arteriovenous malformations (AVMs) is also not straightforward since similar issues plague the few available published trials. The best known (on some counts, infamous) AVM trial is ARUBA, but the study is markedly inadequate in that included were low-grade, surgically curable AVMs randomized to conservative management alone vs. any procedural therapy and studied for a short follow-up duration of 33 months (mean) [17]. This presents another exciting area of research—application of the knowledge gained from multiple studies of AVM treatment modalities (with surgery, embolization, radiosurgery, and combinations) into formulating a trial that combines AVM flow assessment (as opposed to only static morphological parameters) and comprehensive multidisciplinary team-based randomization with recognition of true equipoise. Machine learning algorithms hold promise in this area [18].

Carotid Stenosis

The utility of carotid endarterectomy in symptomatic (>50%) and asymptomatic (>60%) carotid stenosis was demonstrated by NASCET [19], ACAS [20], and ECAS studies [21]. However the increasing application of carotid artery stenting (CAS) has added an element of decision making that has been studied in RCT settings [22]. The concerns with increased periprocedural stroke in CAS are an area of research focus. Possible study designs include incorporating enhanced distal embolic protection devices and longer clinical follow-up to ascertain long-term benefit. Another area of research is the frequent argument that medical management of vascular risk factors has become more aggressive and standardized over the years to the degree that the number of asymptomatic patients with carotid stenosis needed to treat (NNT) with CEA/CAS in order to prevent one stroke may be increasingly higher [23] though improvements have occurred in parallel in surgical technique [24]. A direct comparison between CAS vs. best medical management *and* CEA vs. best medical treatment is being undertaken in the CREST-2 trial that should address this issue. There are also opportunities to incorporate physiological parameters such as carotid plaque morphology and/or flow velocities into similar studies [25, 26].

Occlusive Disease

Treatment for carotid occlusion by EC-IC bypass was deemed to be of no benefit in the recent COSS trial that selected patients based on PET determined hemodynamic (qualitative) flow reduction and randomized them to medical vs. bypass treatment [27]. Yet many flaws noted in that trial need to be addressed with further research [28]. Important among these is the application of rigorous cognitive assessment measures in patients with carotid occlusion given the known effect of hemispheric hypoperfusion in carotid stenosis and occlusion [29–31].

Cognitive status per standardized tools and stratification according to flow reduction (e.g., quantitative rather than qualitative, with use of NOVA measurements) and, thenceforth, comparison of best medical management vs. surgical treatment is a good research focus. Identifying and selecting appropriate candidates for treatment in patients with moyamoya disease based on cognitive assessment and cerebral blood flow measurements is a similar area for potential research [32, 33].

Acute Stroke

Acute ischemic stroke management was revolutionized by the demonstration in multiple randomized trials of the efficacy of endovascular thrombectomy in large intracranial artery occlusion after IV TPA administration [34]. Expanding the pool of eligible patients for IV thrombolysis can also impact the results of stroke therapy if exclusion criteria are narrowed. An example would be the inclusion of patients on novel anticoagulants and accumulating high-quality evidence supporting this [35]. On the other hand, there is an accumulating body of evidence that demonstrates similar outcomes in patients who are TPA ineligible that undergo endovascular clot retrieval [36, 37]. This is a fertile area of investigation because if demonstrated with level 1 evidence, intravenous thrombolysis-related complications might be eliminated in this patient population.

The benefit of endovascular recanalization in occlusion at the level of the M2 vessels remains to be demonstrated. Recanalization of a dominant M2 has the obvious potential of improving speech outcomes, for example, and should be aggressively evaluated [38].

Perioperative Morbidity Reduction

Periprocedural complications can be reduced with attention to pre-, intra-, and postoperative management. Interventions for reducing surgical complications begin in the preoperative phase. An example is smoking cessation before general anesthesia to reduce lung complications and improve wound healing [39]. Another area of research into periprocedural complications is VTE prophylaxis—a recent meta-analysis noted the relative risks and benefits of prophylactic anticoagulation in terms of number needed to treat to prevent DVT/PE/VTE at the expense of increased risk of ICH [40]. The specific indication for craniotomy has not been found to have any correlation with VTE risk [41] but research into the role of prophylactic anticoagulation in procedures such as aneurysm clipping and AVM resection will help understand risk-benefit ratios in vascular neurosurgery which are likely different from tumor or trauma surgery.

Prevention of ischemic complications in aneurysm clipping has relied on intraoperative monitoring with evoked potentials and/or EEG and vessel imaging with ICG [42]. However, no randomized study has established the utility of combined modalities and the stage of surgery when a particular modality may be more applicable. This lends itself to a potential multicenter study of how to best utilize SEP, MEP, ICG,

microvascular Doppler, EEG, and other simpler modalities such as near infrared spectroscopy (NIRS). Another important facet of improving safety of aneurysm clipping is improved visualization of arterial anatomy. Incorporating smaller and more flexible endoscopes is an area of research to minimize morbidity [43]. Another area of research is studying ways of broadening the indications for novel minimally invasive approaches for aneurysm occlusion such as endonasal endoscopic techniques [44].

Wide-necked aneurysms are traditionally treated with clip reconstruction or flow diversion. Newer devices such as the WEB (Sequent Medical, Aliso Viejo, California) or pCONUS device (Phenox, Bochum, Germany) are being introduced for treatment of wide-necked bifurcation aneurysms. Despite promising early results, sound long-term studies are paramount in ensuring continued aneurysm occlusion.

An area often relegated to the background in the "heat of battle" is intraoperative radiation exposure to the surgical team and the patient. This is of immediate relevance to the neurovascular team. Typical exposures vary from diagnostic angiography, Dose Area Product (DAP) 102.4/Kerma-Area Product (KAP) 142.10/0.8–19.6 (5.0) mSv, to higher doses for interventional procedures, DAP 160–172/KAP 382.80 [45]. Reduction of radiation doses requires appropriate use of protective equipment and change in machine settings [46]. Research into better and less cumbersome protection equipment with newer materials is required [47]. Another interesting avenue is the investigation and application of MR angiography as a substitute for diagnosis [48, 49] and ultimately for endovascular therapy [50].

Follow-Up

An important shortcoming of some recent trials has been the lack of adequate data both in terms of length and quality. When such studies end up denouncing therapy altogether or recommend one preferentially over the other, potentially fatal errors of omission and commission occur. The ARUBA trial followed AVMs for a mean duration of less than 3 years for a lifelong disease in patients whose mean age was only in the mid-40s [51]. The implication is denial of potentially curative therapy for seizure patients with grade 1 and 2 AVMs, some of whom may be battling toxic side effects of multiple drugs for seizure control. This clearly demonstrates the need for longer follow-up in studies and disease registries. The COSS trial also followed patients only for 2 years, while there have been reports of progressive hemodynamic insufficiency leading to poor outcomes [52]. In addition, cognitive outcomes were not documented as diligently as stroke/TIA events [53].

For the individual neurovascular patient, research into ensuring close and continued follow-up through behavioral intervention is important. For example, there is roughly 6–10% risk of restenosis 2–5 years after carotid intervention and an elevated stroke risk in these patients compared to those without restenosis [54, 55]. Similarly, there is a definite risk of long-term (10 years) recurrence of aneurysms after coiling requiring retreatment which mandates diligent follow-up [56, 57].

Complication Avoidance Through Simulation

A clear understanding of the positional relationship between various cerebral structures, cranial nerves, and blood vessels is difficult to appreciate on two-dimensional radiographic imaging. For example, the complexity of cerebral vasculature around an aneurysm requires both extensive and exhaustive mental visualization by the treating neurosurgeon. Any error in navigating this complex anatomy may result in potentially fatal consequences for the patient [58]. Also, some neurosurgical cases allow for only one neurosurgeon to operate at a given moment. This is especially true for skull base procedures which have a very small and narrow surgical field of access [58]. Therefore, it would be prudent to practice on anatomically tailored models using 3D printing technology to better understand the anatomic relationships between the lesion and the surrounding normal structures. Many reports on simulation have emerged which have evaluated the utility of 3D printing and virtual reality (VR) in the field of neurosurgery [59]. The use of 3D printer to construct patient-specific three-dimensional models based on actual surgical brain pathology is called rapid prototyping [60]. This technology uses processed 3D images (e.g., 3D-CTA, 3D-DSA) to fabricate patient-specific 3D models. This has been further possible with the digitalization of radiographic images which converts a normal two-dimensional image into 3D [60].

Simulation helps surgeons rehearse delicate surgical maneuvers prior to the actual surgery. In addition, simulation can enhance the training opportunities for neurosurgical trainees as the former have declined due to various factors. Recently, several reports have been published which have evaluated the role of a virtual reality (VR) neurosurgical simulator with haptic feedback in practicing and perfecting techniques [61]. Yet cost can be a barrier to widespread adoption of VR technology, at least at present. Consequently physical models in combination with pre- and posttest objective assessment hold great potential in technique simulation in vascular neurosurgery. Such simulation modules have been developed by the Congress of Neurological Surgeons (CNS) along with scales to assess the performance of students in different types of neurosurgical procedures. The NOMAT (Northwestern Objective Assessment Tool) is a practical example of such a scale that accompanies the CNS Microanastomosis module [62]. Validation studies of NOMAT scale have documented that the scale can reliably distinguish between various levels of performance exhibited by residents at different levels of training [62]. Limitations do exist. For example, it is difficult to 3D print the consistency of different types of aneurysms such as calcified, mycotic, or thrombotic components. Secondly, real-time complications like aneurysm rupture or tearing of friable tissues cannot be simulated effectively. Additionally, it is challenging to recreate the haptics and feedback of different microsurgical techniques. Progressive technological improvements in augmented reality and computing, including via high-end gaming platforms, is an area for active research.

Conclusion

Most complications can be viewed as errors of omission or commission that can impact a patient during disease screening, selection for treatment, surgical intervention, or follow-up. Multiple avenues may be exploited in the study of complications occurring in different stages of disease management in the cerebrovascular patient. Although no single research technique can guarantee a 100% avoidance in complications, the cumulative results of various techniques can provide trainees and surgeons a road map or a blueprint for improving patient outcomes in the field of neurovascular surgery.

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