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

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Learning health systems for innovative neurosurgery – an ethical obligation?

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Introduction

Neurosurgical innovation and continuous evaluation and improvement of neurosurgical procedures are essential to ensure the best level of care for current and future patients. This however, poses a challenge to current neurosurgical practice, as the use of powerful research designs, such as the randomized controlled trial (RCT) are often infeasible for procedures that are now widely considered to be effective.[4,20] This stresses the need for alternative methods to evaluate and compare the efficacy of novel and existing neurosurgical procedures.

In 2007, the Institute of Medicine – an American institution that provides independent analysis and advice in complex problems related to medicine – proposed the learning health systems (LHS), health care systems in which "knowledge generation is so embedded into the practice of medicine that it is the natural outgrowth

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and product of the healthcare delivery process and leads to the continuous improvement of care".[22,2] Key components of the LHS include the search for alternatives to the RCT, implementation of system databases and universal electronic health records, and increasing public and professional understanding of the nature of evidence-based medicine. Whereas LHS aim to facilitate continuous learning activities by integrating clinical research and clinical care, some have noted that too much focus on learning may conflict with a patient's best interests.[2] In this opinionated piece, we discuss how the LHS and associated ethics framework could improve the evaluation of novel and existing neurosurgical procedures, while minimizing potential risks associated with blurring the traditional boundaries between research and care.

Learning health systems in innovative neurosurgery

Alternative trial design

The randomized controlled trial (RCT) is widely regarded as the most powerful research design, and in an ideal world, all neurosurgical trials would be conducted with a form of randomization.[29] In contrast to the introduction of novel pharmaceuticals, however, novel neurosurgical procedures often develop gradually, resulting from an accumulation of minor changes to an established procedure, which are then identified as "novel" in retrospect.[21] For example, endonasal endoscopic pituitary resection* could be seen as a procedure that gradually evolved from microscopic resection*, rather than as a complete new entity.[13] This gradual development often results in "believers", who early adopt the novel procedure, and "sceptics", who will adopt the novel procedure once the long-term outcomes have become available. This may be the reason that endonasal resection* has replaced microscopic resection* in most centers, but not everywhere. Also, many novel neurosurgical procedures are not systematically evaluated during the early developmental stages, which results in a lack of robust evidence, further fueling the debate.[21] Early believers may find it unethical to expose their patients to the shortcomings of the traditional standard of care, whereas the sceptics do not want to expose their patients to potential detrimental complications. Due to this perceived lack of clinical equipoise, it is often very challenging to start an RCT.

From an LHS perspective, several alternatives have been proposed to the randomized controlled study design to evaluate clinical care and innovation, including the cluster randomized trial (CRT).[22] CRTs do not require randomization at patient level but allow participating institutions to perform their preferred standard of care, enabling comparison of practices between different centers. Despite its advantages, a CRT may not to be as effective as an RCT as far greater numbers of patients are required. In addition, centers participating in the CRT would, ultimately, have to change their practice to the superior practice identified at another center at some point.

Another alternative to the RCT is comparative effectiveness research (CER), which allows for the evaluation of chain care to identify superior strategies with regard to patient outcome.[19] Non-experimental CER uses variability in treatment for comparison in real-world conditions and is increasingly used in medicine to compare the

outcomes of different treatments. Examples include the ongoing CENTER-TBI study and a UK trauma registry study that demonstrated the effectiveness of managing patients with severe TBI in neurosurgical centres.[24,19] Pragmatic randomized trials offer another potentially important methodological approach to CER (so-called experimental CER). Probably the most attractive attribute of pragmatic randomized trials is that they aim to balance internal validity and external generalizability, whilst at the same time maintaining the benefits of randomization. An example is the acute subdural hematoma (RESCUE-ASDH) trial.[10]

The above-mentioned research designs may allow neurosurgeons to continue improving their practice and procedures without implementing changes that would have been imposed by an RCT. This makes the perceived lack of clinical equipoise less of a challenge. Naturally, the CER study design has several limitations as it strongly depends on outcomes that are deemed relevant and robust statistical techniques in order to deal with the bias that arises from the absence of randomization. Moreover, there is currently little experience with these research designs in neurosurgery. Nevertheless, it seems preferable to supplement evidence from RCTs with high-quality nonrandomized studies.[22] Therefore, these alternatives could improve evidence-based neurosurgical care but warrant more experience.

Structured data sharing and collection

All potential innovations in neurosurgery require extensive evaluation based on valid data. Despite the variability inherent to many neurosurgical procedures, there is, of yet, no method to systematically register surgical details and patient outcomes for inter-surgeon and inter-center comparisons. Adequate registration and sharing of this data would potentially enhance the generation of evidence by comparative effectiveness research. In addition, ethical problems may arise when research findings are not shared among institutions. For instance, the beneficial results following a minor adaptation to an established procedure may just be verbally transmitted among neurosurgeons within the same institution, without providing the results to the international neurosurgical community, potentially leading to an unjust distribution of beneficial findings. This is especially true for negative research findings, which are often not published (also known as publication bias).[30]

The LHS fosters the implementation of large system databases and universal electronic health records, thereby providing a platform for continuous learning based on clinical decision-making. The LHS regards data as public domain and a central source for advancing knowledge and care. For neurosurgery, this could include systematic registration of information relevant to neurosurgery such as presenting neurological symptoms, imaging details, tumor-related factors, surgical details, complications, costs associated with care, and patient reported outcome measures. Several efforts to share data generated during neurosurgical practice have been made.[12,23,6,28,27] The resulting databases, however, significantly vary in the variables collected, collectors, reliability, and completeness of data, and miss disease-specific variables relevant to neurosurgery.[12] As a result, these datasets currently do not allow for evaluation of learning curves or comparison between different centers, stressing the need for continuous improvement of data registration and sharing to provide valuable insights

that might benefit patients. Nevertheless, differences in outcomes between different institutions can sometimes be evaluated through databases that do not primarily collect neurosurgical data as seen with data from the Trauma Audit and Research Network that was evaluated for traumatic brain injury.[17] One major issue in routine data registration and sharing is that patients have to be informed that they are part of a system in which their data are routinely collected and learned from, and that they consent to this. This makes patient engagement is essential in an LHS.[5]

Patient participation

It can be ethically sensitive to obtain informed consent for data registries[11], which would requires full disclosure, a patient that is capable to make autonomous decisions, and voluntariness.[1] Patients and neurosurgeons may be compelled to do whatever it takes to prolong survival and palliate suffering and may stimulate patient patients to consent to participating in a research activity. The informed consent process may further be complicated when the disease affects the decision-making capacity of the patient, as frequently seen in glioma patients.[8] Neurosurgery is also a highly specialized discipline that is culturally surrounded by prestige.[8] This may give rise to a form of self-coercion, where patients choose to participate in a research activity because they think their doctor believes it is in their best interest.[3] Patients participating in clinical research often misconceive a research activity to be a form of clinical care tailored to their individual medical needs (the so-called "therapeutic misconception").[18] Patients may expect to receive certain benefits from participating in a trial or an observational treatment comparison, while only future patients are likely to experience benefit.[14] The neurosurgeon may also not be aware that an adjustment of a procedure to a patient's specific needs may be considered research by others which further complicates this misconception. The overly optimistic expectancy of a certain research activity is particularly prevalent in neurosurgical innovation, where media reports are generally biased towards success stories, rather than the potential risks involved.[8,25] The opposite may also occur when doctors overemphasize the potential risks associated with a research activity to counteract a patient's optimistic expectations.

The LHS may help to overcome these challenges by "improving public understanding of the nature of evidence-based medicine and the importance of supporting progress toward medical care that reflects the best evidence".[22] Increased public awareness of the nature of evidence-based medicine could potentially lessen the "therapeutic misconception" and smoothen the informed consent process, as informed patients would be able to take a general stance toward participating in research activities before the circumstances arise. Communication to the public is of special importance because the introduction of an LHS is not possible without the trust of patients and referrers, especially when it would mean that patients also have obligations to contribute to improving the quality of care, and cannot always dissent to participation (for instance to be part of a registry).[7,26] In addition, the LHS encourages health care workers to adopt an open attitude towards evidence generation and self-reflection, thereby minimizing the influence of personal interests on the informed consent procedure.

Discussion

Although the LHS may provide a promising way to facilitate neurosurgical innovation and the continuous evaluation of neurosurgical procedures, neurosurgeons should be aware that tempering the traditional divide between clinical research and clinical care may give rise to ethical challenges. Over the last few decades, clinical care and clinical research have been strictly separated.[14] Due to its aim to create generalizable knowledge, research is generally not aiming to benefit a specific individual, and therefore requires specific ethical consideration and regulation in order to prevent individual patients from being exposed to disproportionate risks. To bridge the traditional divide between clinical and research ethics, a new ethics framework has been proposed by Faden and colleagues.[7] The framework aims to stimulate the transformation to an LHS, while ensuring that learning activities within such system are conducted in an ethically appropriate manner. Importantly, it rejects the notion that clinical research and care are ethically distinct entities, and instead provides a set of moral obligations to guide ethically sound research conducted within an LHS.[7,14] This set of moral obligations significantly departs from traditional bioethics in two ways: it places a moral emphasis on learning for both healthcare professionals and patients, even though some have argued that a moral obligation to patients may be problematic.[15] In addition, the framework sets a moral obligation to address unjust distribution of (research) burdens within the healthcare system.[7]

Even though some regard the lack of regular evaluation of (standard) care as a potential hazard to patients, [7] an LHS may entail the risk of placing too much focus on innovation instead of ensuring patients' safety and autonomy. The moral obligation to learning includes both patients and healthcare professionals and holds that everyone involved in healthcare – both on the receiving and the providing end – has the moral responsibility to contribute to learning activities in order to enhance clinical practice "or the value, quality, or efficiency of the systems, institutions, and modalities through which health care services are provided" to the benefit of future patients.[7]

This approach may somewhat temper traditional guidelines of ethical oversight and consent, thereby stimulating continuous learning activities to take place through the implementation of large system databases and data sharing. In addition, active engagement with full disclosure from the neurosurgical community is necessary to respect the autonomy of patients. This could be achieved through a partially standardized disclosure and patient education to make patients active participants in the improvement process. This would require a culture of transparency, open communication, and active engagement towards patients to ensure patients continue to place their trust with the neurosurgeon.

The moral obligation to address unjust inequalities, proposed by Faden et al., may also help to overcome some of the other challenges of evaluating neurosurgical procedures, namely vulnerability and injustice. Neurosurgeons should realize their responsibility to assess whether risks and burdens of a learning activity fall disproportionally on patients that are already disadvantaged.[7] For instance, brain tumor patients that have to undergo a resection* are particularly vulnerable due to the severity and nature of the disease and treatment. The obligation to justice will help to ensure that the burdens of a learning activity will be fairly distributed among these patients, rather

than placing the burden primarily on the most desperate and refractory individuals.[8] Moreover, the obligation to justice also holds that the learning activity will not disproportionally disadvantage patients that are already socially or economically deprived. We believe that this warrants careful handling by the neurosurgical community and an appropriate form of oversight. It should also be noted that the current initiatives towards an LHS in surgery have not resulted in a potentially increased risk of worse outcomes for patients as all databases only introduced a standard method of prospective registration and evaluate a surgical innovation.[12]

Appropriate oversight

Any form of medical research warrants a form of oversight. As opposed to clinical care, research is generally less beneficial to the individual patient and requires specific ethical consideration and oversight to prevent individual patients from being exposed to disproportionate risks. Several frameworks for ethical surgical research have been suggested, such as the IDEAL Framework which upholds the RCT as the golden standard, but opens a door for alternative trial designs as well.[20] The strict distinction between research and clinical care may pose a challenge to evaluating neurosurgical innovations, as any depart from current practice could be regarded as research and may warrant a form of oversight. Neurosurgical innovation often takes place in the gray area between formal research and clinical care, as innovations may have come about as a result of an alteration to a procedure for a specific patient that turned out to be beneficial and implementable to other patients. Innovations may also come about by extending the reach and pathologies for certain surgical innovations, as seen with endoscopic endonasal resection* of anterior skull base meningiomas.[21] There is currently no oversight in place for this gray area. However, it has been suggested that this should depend on the level of potential risk to patients, with less oversight when risks are low, and more rigorous oversight with increasing risks.[16] We believe it to be impractical to mandate IRB approval for every innovative procedure aimed to improve the outcome of an individual patient. On the other hand, innovations that have gained traction among the neurosurgical community and may be applied to other patients should be evaluated with some form of oversight to ensure safety to patients and methodologically sound evaluation. This innovation could at some point be subjected to formal research as suggested by the IDEAL Framework.[20] However, innovation in neurosurgery may also be subjected to different forms of oversight, such as the neurosurgical department, neurosurgical societies, surgical colleges, or dedicated institutional boards.[9] We believe that oversight in an LHS should be tailored to neurosurgery with great involvement of the neurosurgical community and patient advocacy groups to balance safety of patients and continuous innovation and that the amount of oversight should be guided by the estimated risk of the innovation.

Conclusion

The LHS and its associated ethics framework holds the potential to overcome several challenges associated with neurosurgical innovation. These solutions are primarily formed by alternative trial designs, structured data sharing and collection, and

increased patient participation. Implementation of the LHS, however, comes with ethical challenges specific to neurosurgery that include respect for autonomy, justice to patients and appropriate oversight.

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