

# Epilepsy Surgery in Low and Middle Income Countries: A Scoping Review

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## **Abstract**

**Background:** Epilepsy surgery is an important treatment option for people with drug resistant epilepsy. Although surgical procedures are under-utilized worldwide, it is far worse in Low- and Middle-Income Countries (LMIC) and it is less clear to what extent people with drug resistant epilepsy receive such treatment at all. Here we review the existing evidence for the availability and outcome of epilepsy surgery in LMIC, and discuss some challenges and priority.

**Methods:** We used the six stage methodological framework developed by Arskey and O’Malley as a guide. We searched PubMed, Embase, Global Health Archives, Index Medicus for South East Asia Region (IMSEAR), Index Medicus for Eastern Mediterranean Region (IMEMR), Latin American & Caribbean Health Sciences Literature (LILACS), African Journal Online (AJOL), and African Index Medicus (AIM) to identify the relevant literature.

**Results:** We retrieved 148 articles on epilepsy surgery from 31 countries representing 22% of the 143 LMIC. Epilepsy surgery appears established in some of these centers in Asia and Latin America, while some are in their embryonic stage reporting procedures in a small cohort performed mostly by motivated neurosurgeons. The commonest surgical procedure reported was temporal lobectomies. The post-operative seizure-free rates and quality of life are comparable to those in the high-income countries (HIC). Some models have shown that epilepsy surgery can be performed within a resource-limited setting through collaboration with international partners and through the use of information and communication technology. The cost of surgery is a fraction of what is available in HIC.

**Conclusion:** This review has demonstrated the availability of epilepsy surgery in few LMIC. The information available is inadequate to make any reasonable conclusion of its existence as routine practice. Collaborations with international partners can provide an opportunity to bring high-quality academic training and technological transfer directly to surgeons working in these regions and should be encouraged.

**Keywords:** Epilepsy; Surgery; Low- and Middle-Income Countries; Access; Priority

## **1.0 Introduction**

About a third of people with epilepsy continue to have uncontrolled seizures despite adequate and appropriate medical treatment [1, 2]. These persons with medically intractable epilepsy have a poorer quality of life (QOL), increased risk of injury and cognitive decline, poor psychosocial outlook and an increased chance of death compared to their seizure-free counterparts [3-6]. Over the last decades various epilepsy surgery techniques have evolved to become major treatment options, but they are underutilized [7]. The benefits of these surgeries outweigh the associated risks in achieving seizure freedom, improving quality of life and reducing mortality [8-17]; with about 60% of those who had temporal lobe resective surgery remaining seizure-free in the long-term [18, 19].

The extent of epilepsy surgery utilization, outcome and cost are not well known in Low- and Middle-Income Countries (LMIC). A global survey between 1980 and 1990 reported few published literature from LMIC and none from Africa [20]. By the end of 1999, epilepsy surgery was present in only 26 (18.3%) of 142 LMICs [21]. Whether the high ‘surgical treatment gap’ is due to mere exclusions from international surveys or underreporting of surgical practices, it is certain that underutilization is a more serious problem in LMIC than high-income countries (HIC), with the majority of health centers lacking the capacity to perform neurosurgery or even non-existent and most health personnel referring surgical candidates elsewhere [22].

Some of the most important factors for the high surgical treatment gap are the lack of organized structured care, lack of infrastructure, shortage of specialists and the cost of surgery [21, 23-25]. A recent review observed that barriers to epilepsy surgery are perpetuated by the uncertainty portrayed by medical practitioners towards surgical treatments, reflecting the knowledge gap, which may be more pervasive in LMIC [26]. With the increasing evidence of surgery as an important treatment option and the higher burden of epilepsy, it is important for health care providers and users in LMIC to know that there is more that can be done. At the same time, however, information on the availability of epilepsy surgery is scarce. This scoping review therefore aims to: i) identify the availability of epilepsy surgery in LMIC; ii) determine the resources available at these centers; iii)

determine the outcome and cost of surgical procedures; and iv) discuss the challenges and possible areas for potentially closing the surgical treatment gap in resource poor settings.

## **2.0 Methodology**

This review was triggered by a growing concern on the standard of care for people with drug resistant epilepsy in LMIC. We considered various systematic approaches to review the literature on utilization of epilepsy surgery in these countries and decided to undertake a scoping review. We proposed that a scoping review will be an appropriate strategy to review and summarize a range of evidence in order to convey the breadth and depth of this less understood treatment option [27]. A scoping study was preferred over a systematic review or meta-analysis as it allows a range of study with varying designs to be incorporated without assessing the quality or using a systematic analytical interpretation of the literature [28]. A scoping review was therefore found to be ideal to help clarify surgical alternatives for people with medically intractable epilepsy in resource poor settings. We adopted the six stage methodological framework developed by Arksey and O'Malley [27]. This includes: (1) identifying the research questions; (2) identifying relevant studies; (3) selecting the appropriate studies; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) a consultation exercise with key stakeholders to inform and validate study findings.

### **2.1 Identifying the research questions**

This review's primary interest was to map and broadly examine the literature on epilepsy surgery in LMIC. In order to do so we identified some research questions to guide our scope.

1. What is available regarding epilepsy surgery in LMIC from published literature?
2. What are the types of surgeries and outcomes, QOL and cost?
3. How important is collaboration and technological transfer between HIC and LMIC?

### **2.2 Identifying the relevant studies**

We identified papers using the following databases: PubMed, Embase, Global Health Archives, Index Medicus for South East Asia Region (IMSEAR), Index Medicus for Eastern Mediterranean Region

(IMEMR), Latin American & Caribbean Health Sciences Literature (LILACS), Western Pacific Region Index Medicus (WPRIM) and African Index Medicus (AIM) via the WHO Global Index Medicus, and the African Journal Online (AJOL). The search was made using various combinations of the following key words “epilepsy” and “surgery” or “surgical” or “surgical procedures” or “resecti\*” or “disconnecti\*”, or “neurostimulati\*” and individual LMICs according to the World Bank classification ([www.worldbank.org](http://www.worldbank.org)). Medical subject headings (MeSH) were used where appropriate and the references within each article were also reviewed to obtain further information (see Supplement 1 for the detailed search strategy). We included observational studies, clinical trials, case series and any publication reporting the conduct of epilepsy surgery, outcomes (based on the Engel classification or equivalent), mortality, complication, QOL or costs. Epilepsy surgery was defined as procedures undertaken mainly to control drug-resistant epilepsy as opposed to removing an acquired structural brain lesion. The surgical procedures include resective, disconnective, or neurostimulative surgical modalities, irrespective of year of publication or language.

Studies reporting neurosurgeries offered exclusively for brain tumors, infections and other conditions not associated with epilepsy were excluded. Although, reviews, meta-analysis, single case reports, letters, commentaries and editorials were excluded; they helped give a lead to relevant publications.

### **2.3 Study selection**

We used a two-stage selection process. The initial selection process (done by MMW) involved the review of title and abstract to determine those likely to be eligible. The second part of the selection process involved two independent reviewers (MMW and FX), who reviewed the potentially eligible papers in more details resorting to abstracts and full articles. No study was excluded based on language as the authors understand the major languages spoken in the regions.

### **2.4 Charting the data**

In order to have a clear focus on the charting process, a data-charting form was developed to extract information from the literature (Table 1). The data-charting form was developed from the revised version of quality guidelines for pre-surgical epilepsy evaluation and surgical epilepsy treatment by

the Austrian, German, and Swiss working group [29]. The aim of the guideline is to instruct on the minimum standard requirement for running an epilepsy surgery facility. This served as a guide to understand what is available from LMIC, as what is a minimum requirement in Europe may not be the same elsewhere in LMIC [30].

## **2.5 Collating, summarizing, and reporting the results**

We collected and sorted key information from the eligible articles and summarized them in tables. The key information in addition to the minimum standard requirements; include author, year of publication, name of center and country, period of recruitment, types of surgeries, number operated, follow-up duration, outcome measures, mortality, complications, collaborations, QOL and cost. Where available the outcomes from neurostimulative procedures like vagus nerve stimulation (VNS) were recorded. A narrative review was also used to report other information. We recognize the inherent challenges with retrieving data from LMIC due to varying methodologies of the papers and their reporting guidelines, therefore some of the information we report have been derived from multiple articles and sources.

Various outcome measures are being used by surgeons, but we retrieved those reporting either the Engel or ILAE outcome classifications. The differences and their utility have been discussed in the ILAE commission report on classification of outcome following epilepsy surgery [31]. The Engel classification is used widely, but results from different centers may not be easily compared, while the ILAE classification is easier to use. Both the ILAE and the Engel classification, however, have a good inter-rater reliability and significant correlation between the two [32] (Supplement 2 shows details of the outcome scores).

## **2.6 Consultation with key stakeholders**

The optional stakeholder meeting was not conducted due to lack of funding. This work is an iterative work in progress and findings should guide stakeholders on action areas and determine where in-depth analysis is required.

### **3.0 Results**

The initial search identified a total of 1,365 publications, 158 duplicates were removed, while 201 full texts articles were assessed for eligibility. During the review 53 potentially eligible studies were excluded. These included neurosurgical procedures for tumors, infections and others that cannot be classified as epilepsy surgery. In addition some were conference abstracts that had incomplete information and were difficult to extract (Figure 1 shows flowchart of the selection process). A total of 148 publications from 31 countries met the eligibility criteria; representing 21.7% of the 143 LMIC as shown in Table 2 [33-180]. The information retrieved was from published journal articles and some website sources. The publications were mainly longitudinal studies, case-series, case-control studies and one randomized controlled study. They include nine publications from six African countries [33-42]; 52 publications from 12 Latin American and the Caribbean countries [43-94]; 85 publications from 13 Asian countries [83, 94-177] and three publications from two Eastern European countries [178-180]. The bulk of the published literatures are from India, China, and Brazil. The papers retrieved spanned over 60 years, but only seven papers were published before the year 2000. A closer look at some of these papers especially from India, Brazil and China reveal multiple publications from the same cohort. These publications show that a more recent paper incorporates subjects or is a subset of a cohort reported from older papers.

The results on the minimum standard requirements (Table 2) showed that most centers had the minimum technical equipment. Information on whether they had sufficient qualified personnel or adequate training was mainly not mentioned or difficult to extract. Some papers reported on collaborative work between HIC and LMIC in Uganda [36-38], Tunisia [41], Thailand, India and Argentina [83, 105], Pakistan [168], and Iran [171]. The collaborative epilepsy surgery program between North America and the CURE Children's Hospital of Uganda (CCHU) assessed the feasibility of an epilepsy surgery program in a resource-poor setting using just video-electroencephalography (EEG) and computed tomography (CT) volumetric analysis [38]. The Tunisian epilepsy surgery program at the Charles Nicolle Hospital Tunis and the French hospital at Rouen via the EUMEDCONNECT, is an internet network project where clinical, EEG and radiological information are transferred from Tunis to France for discussion and evaluation [41].

Detailed illustration of the general characteristics, outcomes measures, complications and mortality is shown in Supplement 3. Table 3 shows the general characteristics of 98 papers reporting outcome measures of various epilepsy surgeries according to either the Engel or ILAE classifications. The commonest surgeries performed at these centers are temporal and extra-temporal resective surgeries, disconnective surgeries like corpus callosotomies, hemispherectomies and sub-pial resections. The varying reporting methods, number of candidates, classification of surgery type and the duration of follow-up made reporting our results on outcome difficult. The majority reported outcome measures based on the Engel classification. The reported outcome measures ranged mostly between 40% to 80% (for Engel Class I) and 50% to 90% (for Engel Class I and II) in carefully selected subjects. Complications are transient or minor; while major complications or mortality is rare. These results appear better for temporal lobe surgeries. Table 4 shows neurostimulative techniques like VNS [57, 86, 120, 138, 151, 157, 173] and deep brain stimulation [73], which reflected that the majority of subjects had more than 50% seizure reduction with follow-ups ranging between one to four years. Table 5 showed that the indicators of QOL improved after surgery [37, 47, 50, 59, 93, 98, 101, 122, 126, 134, 159, 160, 165, 175, 177], except in one study [62].

Table 6 reports on the cost of epilepsy surgery [66, 70, 71, 114, 117, 144, 147, 164, 168, 171, 172] and VNS [138], the cost of epilepsy surgery as at 2014 ranges between US\$500 in Iran to approximately US\$8,000 in China.

#### **4.0 Discussion**

This scoping review was undertaken to assess the situation of epilepsy surgery in LMIC. The current status of published evidence reports epilepsy surgery in about a fifth of LMIC. Our findings suggest that the utilization of epilepsy surgery has evolved considerably in some centers in Asia and Latin America with an increasing trend in places like India, China and Brazil [182] but appears embryonic in some other countries, particularly in sub-Saharan Africa. A large proportion of the retrieved papers are case series or experiences using small sample size of carefully selected candidates performed by motivated neurosurgeons and may not necessarily portray that epilepsy surgery is an established current practice in these countries. We observed that epilepsy centers were not evenly distributed, but

located in bigger more affluent cities. This geographical disparity has been observed in a previous review [21]. A review of epilepsy surgery in India showed that geographical disparity is a common problem, and only 2 centers in big cities contributed to more than 50% of 420 surgeries performed annually, which is far from adequate [183].

The surgeries reported were mainly resective, few disconnective, and much fewer neuro-stimulative techniques. The commonest surgery was for temporal lobe epilepsy; this may have been targeted because it impacts the greatest and has an excellent opportunity for seizure freedom from clinical trials [18]. It is noteworthy to observe that the seizure outcome after surgery was good in the majority of subjects and comparable to other centers in HIC. Similarly, complications and mortalities from surgery did not appear to be significantly different from those reported in HIC [17, 184]. Those that had surgery also had an improved QOL, employability and lower perceived stigma compared to those who did not, especially for those who were seizure free [37, 50, 159]. The similar short-term outcome rates in LMIC compared with HIC may be due to centers performing straight forward cases in carefully selected candidates. It will be important to know the longer-term outcome of these surgical candidates, but some of the studies had a high loss to follow-up which is a common problem in LMIC [185].

Some of the established centers had adequate infrastructure, manpower and training, but this is not universal. The Ugandan experience shows that the lack of sophisticated modern equipment should not be a limitation to surgery [36, 38]. Their model utilized technology and expertise that was reasonably available and could function sustainably in resource-poor setting. Training was possible through the establishment of collaborations with neurosurgeons in HIC. This form of collaboration where expert skill and knowledge were exchanged with centers in the West was also noted at the Charles Nicolle Hospital in Tunisia [41], the Aga Khan University Hospital in Pakistan [167] and the Shiraz University of Medical Sciences in Iran [171]. The successes of these models were achieved through the tri-faceted approach of technological transfer, twinning, and manpower training [30]. It also shows the role information and communications technology (ICT) can play in intellectual and skills transfer, showing that the model used could be replicated elsewhere. With comparable seizure-free rates to HIC, these surgical experiences give hope that epilepsy surgery can be a routine treatment

using the minimum available requirements that are more likely to be available in LMIC in comparison to the myriad of equipment used in more affluent societies for epilepsy surgeries. The Pediatric Epilepsy Surgery Task Force of the ILAE Commissions of Pediatrics and Diagnostics in formulating recommendations for pre-surgical evaluation in children observed that many of the tests employed is resource intense, and that failure to carry out all diagnostic tests possible nor insisting on one particular ancillary test should not hamper the conduct of surgery. They suggested that evaluation should be done according to the needs of the clinical cohorts and country-specific resources [186]. The training of personnel in view of the profound manpower shortages in LMIC can be done through collaborations with experts from HIC [187].

The cost of epilepsy surgery reported in this review is a fraction of what it cost in western countries [71]. The issues of cost and affordability are not straightforward [188], as what is regarded as cheap may not necessarily be affordable to the majority of people in LMIC, as those who access this care are probably city dwellers, more educated and of higher socioeconomic class [26]. Epilepsy surgery is an expensive venture requiring some of the most expensive technologies in the surgical field and therefore establishing neurosurgical centers is a challenge for most LMIC with an already dysfunctional primary care system and the majority of persons unable to access first line antiepileptic drugs. In view of the high burden of epilepsy in LMIC, it is debated whether surgery may be a cost-effective long-term investment that may benefit more people in the long run [188]. Studies evaluating the costs of surgical versus medical treatment observed that although surgical treatment requires a large initial expenditure it was superior because of the greater seizure-free rate, with the long term cost-analysis favoring surgery as the cost-time curves intersect in a few years [189-191]. These cost-analyses comparing medical and surgical therapy of epilepsy should be interpreted with caution since the cost of surgery and benefit gained by seizure reduction are not linear and that measuring just the reduction in seizure frequency in the short-term is inadequate to compare costs. The benefit of epilepsy surgery to a substantial number of persons in LMIC, however, may outweigh the cost with regards to the transformative power of a seizure-free life. The capacity to empower a sufferer and the community, restoration of livelihood and the contribution to the local economy by freeing the caregiver and family from the economic and social burden may be reasons to prioritize epilepsy surgery

[188]. Cost-effectiveness of epilepsy surgery should be an area for further studies, as analyses from HIC may not reflect the situation in LMIC due to the weak economic capacity and regional complexities. The equity proposed for people with epilepsy is usually jeopardized by causes of inequality such as poverty, illiteracy and the marked urban-rural disparities which are deep-rooted and difficult to control in the poorer regions [192]. Strengthening primary health care, improving the referral pathway and expanding health insurance coverage may help diminish this inequality [193-195]. The provision of epilepsy surgery may sometimes not correlate with a country's socioeconomic status, since the higher the gross domestic product the higher the health expenditure. For example some Middle Eastern countries may not have a problem with infrastructure, but may lack expertise, while African countries are more likely to have problems with both.

Lesion-related epilepsies may be higher in LMIC. The high prevalence of febrile seizures, malaria and other CNS infestations may act as initial precipitating injury for developing hippocampal sclerosis [196]. An important research priority will be to investigate the burden of lesion-related epilepsy and the number of potential surgical candidates within a geographical context. This could make a case that epilepsy surgery may have been unfairly neglected compared to surgical treatment of other public health conditions [197]. Health care providers also have an ethical obligation to identify and facilitate access to epilepsy surgery for these vulnerable subgroups [198]. Whether minimally invasive surgeries may be a cost effective or efficacious option is an ongoing discussion, as subjects may be more willing to undergo minimally-invasive procedures due to lower perceived risks [199].

Several limitations are noted in this scoping analysis. Firstly, this review may not necessarily reflect all epilepsy surgeries performed in LMIC, as we have information from only 22% of countries. Due to the difficulty in retrieving literature from LMICs we may have excluded relevant information outside of our search. Unfavorable results of epilepsy surgery are also less likely to be published in journal articles. Secondly, it was difficult comparing results across board, based on the varying facilities, differing methodological approaches, lack of uniformity in reporting outcome measures and different follow-up times. The use of international standardized methods for future work would help improve comparability [29]. International multicenter studies involving some LMIC prove that it is possible to produce an evidence-based practice with good quality data [83, 105]. Thirdly, despite attempting to

use a consistent clear approach following the scoping analysis framework [27], one of the problems we encountered is that the current available literature does not give holistic information. Some articles were excluded from the final analysis because of lack of access to the full text, although reviewing these abstracts substantiated the findings that some are conference abstracts from previous works. We also excluded articles reporting other neurosurgical procedures; however these papers may indicate a center's potential technical expertise to perform epilepsy surgery if given the necessary support and improvement. Fourthly, a stake holders meeting which is the sixth optional item of the scoping framework was not done. Our experiences from this review have shown that it is a necessary requirement and it would have been good to interact with the two stakeholder groups – the service providers and users. For example, we observed that the lack of data on the number of qualified personnel and staff training from the literature retrieved was considerable. Interaction with stakeholders and a visit to these centers would have given a first-hand assessment of what surgical facilities are available and not just relying on published articles. An alternative to a stakeholders meeting would have been to send questionnaires to the centers. Lastly, we did not retrieve information on referral pattern and how PWE access surgical options and how long it took, this would have been important to understand barriers from the health user's point of view. Understanding the structural, cultural, financial and political barriers limiting epilepsy surgery will be an important initial step in prioritizing epilepsy surgery.

## 5.0 Conclusion

This review demonstrates the availability of surgical treatment for epilepsy in some LMIC, with an increasing trend in a few. Some experiences have shown that epilepsy surgery can be performed within the resource-poor settings through collaboration with international partners. ICT can be an important tool for skill transfer. These collaborations with international partners can provide an opportunity to bring high-quality academic training and technological transfer directly to surgeons and should be encouraged. The high cost of implementing surgery may not be a limitation to some LMIC countries, but rather a problem of deciding how to prioritize and allocate resources [200]. Governments should weigh the immediate large monetary investment with the long term benefits and

sustainability. We acknowledge the limitation of data acquisition in LMIC; therefore we may not have fully retrieved all the information regarding epilepsy surgery. Even where surgeries are performed, the small number operated and varying reporting methods make any reasonable conclusions regarding its definite continued existence difficult.

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### **Author Contributions**

MMW – Study concept and design, data acquisition, data interpretation, manuscript production; FX – Data acquisition, data interpretation, manuscript production; MRK – Data interpretation, technical input and critical review of manuscript; AM – Data interpretation and critical review of manuscript; ASW – Technical input and critical review of manuscript; AWM - Technical input and critical review of manuscript; JWS – Study concept and design, critical review of manuscript. All authors approved the final version. JWS is the guarantor.

### **Conflict of Interest:**

MMW, FX, AM and ASW have no conflict of interest. MRK receives research support from UCB and Eisai, and has received unrestricted educational grants from UCB and personal fees from UCB, Sage Therapeutics, and Novartis. AWM has received support from UCB, Baxter, and Cyberonics. JWS receives research support from the Marvin Weil Epilepsy Research Fund and the UK Epilepsy Society endows his current position. He has received research funding from Eisai and UCB, personal fees from Eisai, UCB, Bial and Janssen outside of the submitted work.

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