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Review

Systematic review of the efficacy in seizure control and safety of neuronavigation in epilepsy surgery: The need for well-designed prospective studies

Daniele Kanashiro Sonvenso [a], Emerson Nobuyuki Itikawa [a,e], Marcelo Volpon Santos [c], Leonardo Alexandre Santos [a], Ana Carolina Trevisan [a,e], Marino Muxfeldt Bianchin [d], Felipe Arriva Pitella [a], Mery Kato [a], Carlos Gilberto Carlotti Jr. [c,d], Geraldo Filho Busatto [f], Tonicarlo Rodrigues Velasco [d], Antonio Carlos Santos [a,f], João Pereira Leite [d], Américo Ceiki Sakamoto [d], Hélio Rubens Machado [c,d], Altacílio Aparecido Nunes [b], Lauro Wichert-Ana [a,b,e,f,*]

[a] *Nuclear Medicine & Molecular Imaging Section, Image Science and Medical Physics Center, Internal Medicine Department and Post-graduation Program, University of São Paulo, Ribeirão Preto, Brazil*
[b] *Health Technology Assessment Center of the Clinical Hospital, University of São Paulo, Ribeirão Preto, Brazil*
[c] *Clinical Surgery Postgraduate Program, Department of Surgery and Anatomy, University of São Paulo, Ribeirão Preto, Brazil*
[d] *Epilepsy Surgery Center (CIREP), Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil*
[e] *Bioengineering Interunits Program, São Carlos School of Engineering, University of São Paulo, São Carlos, Brazil*
[f] *The Center for Interdisciplinary Research on Applied Neurosciences – NAPNA – University of São Paulo (USP), Brazil*

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ABSTRACT

Purpose: To evaluate the efficacy of surgery with neuronavigation compared to conventional neurosurgical treatment of epilepsy in terms of safety and seizure outcomes and to assess the quality of the evidence base of neuronavigation in this clinical context.

Method: Systematic review using the electronic databases of Cochrane, CRD, PubMed, Embase, SciELO and LILACS in Portuguese, English and Spanish. The [MeSH] terms included "epilepsy" and "neuronavigation". Eligibility Criteria: Studies assessing surgery with neuronavigation for the surgical treatment of epilepsy or brain injuries associated with epileptic seizures.

Results: We identified 28 original articles. All articles yielded scientific evidence of low quality. Outcome data presented in the articles identified was heterogeneous and did not amount to compelling evidence that epilepsy surgery with neuronavigation produces higher rates of seizure control, a reduced need for reoperations, or lower rates of complications or postoperative neurological deficits.

Conclusion: We were unable to find any publications providing convincing evidence that neuronavigation improves outcomes of epilepsy surgery. Whilst this does not mean that neuronavigation cannot improve neurosurgical outcomes in this clinical setting, well-designed research studies evaluating the role of neuronavigation are urgently needed.

1. Introduction

Epilepsy surgery is a therapeutic option for patients whose seizures are refractory to medical therapy, as it may reduce seizure frequency and mortality rates as well as alleviate the psychosocial burden and clinical morbidity associated with epilepsy. Epilepsy surgery aims to remove the epileptogenic zone (EZ), whilst avoiding surgical complications such as motor, visual and cognitive deficits [1]. Therefore, as long as the interference with healthy neural tissue is kept to a minimum, fewer are the risks of post-operative complications.

Modern neuroimaging techniques play an important role in the pre-surgical assessment of epileptic patients, both for decision on surgical approach such as for anatomical outlining of resection

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* Corresponding author at: Seção de Medicina Nuclear, Hospital das Clínicas – FMRP – USP, Av. Bandeirantes, 3900, CEP: 14048-900 Ribeirão Preto, SP, Brazil. Tel.: +55 16 36022596; fax: +55 16 36022596.
E-mail address: lwichert@fmrp.usp.br (L. Wichert-Ana).

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limits, and also to spare eloquent areas and important vascular structures [1]. Specifically, neuronavigation techniques allow better visualization of spatial relationships within the brain invisible to the naked eye using CT, MRI, and angiographic scans [2]. Neuronavigation uses stereotaxy principles, whose main function is to visually show the surgical region of interest by means of a rigid reference system coupled with the patient's scan coordinates system [3–6]. However, even though neuronavigation systems are widely applicable, their accuracy in brain topographic location of the EZ may be curtailed due to the so-called "brain shift" effect, which is the representation of movements or dislocation of the brain parenchyma somewhere between image acquisition and completion of surgery [2]. For instance, merely opening the cranial bone via craniotomy leads to loss of cerebrospinal fluid and subsequently to a new cerebral position. Hence, the surgeon has to deal with a situation in which the organ to be operated on is continuously modified and whose pre-operative scans might become outdated [2]. A way to solve this problem is the acquisition of intra-operative neuroimaging scans such as CT or MRI, or real-time imaging with ultrasonography or fluoroscopy [7].

As a result of these neuronavigation techniques described, one can expect a marked improvement in surgical outcomes, offering two essential parameters of surgical excellence: efficacy and safety [8]. According to the World Health Organization (WHO), efficacy can be defined as the benefit or usefulness to an individual, provided by a service, treatment regimen, medication, prevention or control measures, either advocated or applied [9]. On the other hand, safety represents a value judgment over the acceptability of risk in a specific situation. Risk is the probability of occurrence of an adverse or undesirable effect, and severity of resulting injury to personal health in a defined population, associated with the use of medical technology, under specific conditions [10].

This systematic review aimed to assess the safety and efficacy of neuronavigation for epilepsy surgery in comparison with conventional neurosurgery.

2. Methods

2.1. Eligibility criteria

We searched for controlled trials, blind or non-, randomized or non-, systematic reviews or non-, with or without meta-analysis. The strength of the evidence was evaluated for all included studies using the Oxford Centre for Evidence Based Medicine (OCEBM) [11]. Case or brief reports, forums, technical notes, and opinion articles were excluded.

The PICO (Population, Intervention, Comparison, Outcome) strategy was applied to help guide our search. *Question of Efficacy*: whether neuronavigation (Intervention) had more efficacy for seizure control (Outcome) than conventional neurosurgery (Comparison) in patients who underwent epilepsy surgery (Population). *Question of Safety*: whether neuronavigation (Intervention) had more safety (Outcome) than conventional neurosurgery (Comparison) in patients who underwent epilepsy surgery (Population).

For the *question of efficacy*, studies were selected that described the postoperative control of epileptic seizures based on Engel's Classification. [12]

For the *question of safety*, studies were selected that described the adverse events and complications that occurred during or soon after surgery.

2.2. Information sources

Information sources included MEDLINE, the COCHRANE Library, University of York Centre for Reviews and Dissemination – CRD, Embase, the Latin American and Caribbean Health Sciences database – LILACS, and Scientific Electronic Library Online – SCIELO.

2.3. Search strategy

Medical Subject Headings (MeSH) were used for electronic database searches, from their dates of inception up to 19th August 2014. The primary searches were conducted in three languages: English, Portuguese and Spanish.

The search was conducted in English in MEDLINE, CRD, Embase, the COCHRANE Library, LILACS and SCIELO with the following query: neuronavigation AND epilepsy.

The search was conducted in Portuguese in LILACS and SCIELO with the following query: neuronavegação AND epilepsia.

The search was conducted in Spanish in LILACS and SCIELO with the following query: neuronavegación AND epilepsia.

2.4. Study selection

Study selection was performed independently and blindly by 2 reviewers (D.K.S. and E.N.I.) who retrieved potentially relevant titles and abstracts and transcribed data from eligible studies onto individual datasheets. All articles deemed potentially eligible for inclusion were retrieved in full-text format. Studies published only in abstract form were excluded. Disagreements on study inclusion or endpoints were resolved by a third author (L.W.A.).

Studies were included when evaluating epileptic patients of both sexes, regardless of epileptic syndromes and seizure classifications, ethnicity and age, and diagnosed with pharmacoresistant epilepsy or other injuries associated with seizures, associated or not to epileptogenic or expansive lesions.

Quality of evidence and strength of recommendation were evaluated by the same reviewers for each article using the Scientific Level Evidence Classification based on the type of study [11].

2.5. Data items

Information was extracted from each included study on: (1) Characteristics of studies (authors, year, country of study, and language of publication); (2) Patient details (number of patients, age); (3) Details of surgery (number of patients who underwent surgery, duration of anesthesia between preparation and complete skin incision, operative time, postoperative complications, need for re-resection); (4) Details of postoperative follow-up (duration of postoperative follow-up, length of ICU stay, hospital stay, surgeon's subjective evaluation regarding usefulness of neuronavigation, postoperative complications, postoperative neurologic deficits and surgical outcome according to Engel's classification).

3. Results

3.1. Study Selection

Our search in databases identified 189 articles with the queried keywords. Of these, 176 articles were found in MEDLINE (PubMed), five articles in the Cochrane Database of Systematic Reviews, seven articles in LILACS, one article in SCIELO and none selected from Embase and CRD.

Nine duplicated articles were excluded. We also excluded 24 articles because they were not written in English, Spanish or Portuguese, and another 33 studies because they were not fully available, resulting in 123 articles. These were independently read in full by two of the authors who appraised their suitability for inclusion in the study. A total of 95 studies were excluded because they did not fulfill the eligibility criteria. Finally, 28 studies on the efficacy and safety of neuronavigation were selected for this systematic review. A flowchart of the entire process of systematic review can be seen in Fig. 1.

3.2. Study characteristics

The origin of studies by country was: United States (*n* = 2), Germany (*n* = 8), Canada (*n* = 2), India (*n* = 1), China (*n* = 4), France (*n* = 1), Japan (*n* = 2), Korea (*n* = 1), Italy (*n* = 2), United Kingdom (*n* = 1), Belgium (*n* = 1) and Austria (*n* = 3). Publication dates ranged from 2000 to 2014 and all selected articles were written in English (see Table 1).

Twenty-seven articles presented evidence level 2C and one article level 3B. All the 28 articles have reached grade of recommendation B.

3.3. Casuistic and postoperative follow-up

A total of 704 patients were enrolled in the 28 studies, with a mean of 25.14 patients per study. The total mean age was 52.39 years, ranging from four months to 72 years. Twenty-two out of 28 studies described the postoperative time of follow-up, resulting in a mean of 67.04 months (see Table 1).

3.4. Postoperative seizure control

Actually, only one article, Oertel et al., compared the postoperative seizure control between surgeries with and without neuronavigation [15]. It showed that 52.6% of patients in the neuronavigation group and 63.2% in the non-navigation group remained seizure free after surgery.

In an attempt to estimate the average rate of seizure control after surgery with neuronavigation alone, we analyzed 18 of 28 included studies that described the postoperative Engel's classification for outcome (*n* = 303 patients) (see Table 2). Based on this subgroup of patients, the efficacy in seizure control was 90.36% (Classes I and II) for surgery with neuronavigation. However, a detailed analysis of these studies shows that some authors have the tendency to describe all their series of good results only. More realistically, Cui et al. observed that among 69 patients with focal epilepsy treated by surgery with neuronavigation, 62.31% had a good outcome (Engel I and II) [14]. Meanwhile, five studies excluded from this specific analysis described postoperative status as “free of seizures”, “partial control” or “without control”, and thus not allowing an accurate measurement of postoperative outcomes [15–19]. These studies found that 100% [16,17], 80% [18] and 66.66% [19] of patients became seizure-free after surgery with neuronavigation.

We know that the comparison of averages of efficacy obtained from all observational neuronavigation reports analyzed by this review cannot be compared with a single control group of non-neuronavigation patients described by only one study [15]. They are different cohorts. Based on these data, we believe the efficacy of neuronavigation on seizure control remains unclear.

3.5. Repeated resections

Only five studies described the need for repeated resections, regarding only cases that underwent surgery with neuronavigation. In these studies, for 52.6% [15], 23.07% [20], 25% [21], 47.36% [22] and 60% [23] of patients operated with neuronavigation, the resection was quoted as incomplete after updating neuronavigational data, such as intraoperative MRI, and re-segmentation of residual lesions was needed. However, there is great heterogeneity of clinical and surgical information among these studies. In fact, only Oertel et al. described that after electrocorticography (ECoG), there was need for extension of the temporal lobe resection in 30.6% in the neuronavigation group versus 47.1% in the control group [15]. We would like to reinforce the need for well-designed research projects to evaluate these variables in epileptic patients that will undergo comparative studies about surgery, with and without neuronavigation.

3.6. Subjective analysis of neurosurgeons

Three out of 28 included studies described the subjective and personal opinion of neurosurgeons regarding clinical and surgical utilities of neuronavigation. In the first study, the application of neuronavigation was considered to be helpful by the senior neurosurgeon in 92.7% of cases [15]. In the second study, the intraoperative use of frameless neuronavigation to place electrodes, to locate the lesion or to determine the extent of resection, and to integrate all images to form one dataset, were essential for decision making and helpful in 76% of patients, and judged to be essential to accomplish epilepsy surgery in 28% of cases [24]. In the third study, the surgeon felt the data were helpful and made surgery safer in 100% of 21 patients that underwent anterior temporal lobe resection with neuronavigation [25].

3.7. Operation time

Only one study compared the operation time between the temporal lobe epilepsy surgery with and without neuronavigation, and found a non-significant difference. It reported a mean operation time of 239 min for surgery with neuronavigation and 208 min for non-neuronavigation surgery [15]. Four other studies reported only mean operation times for neuronavigation, 212 min [26], 213.3 min [27], 243 min [19] and 213 min [20], respectively.

3.8. Duration of postoperative in-hospital and in-ICU stay

Only three studies evaluated postoperative in-ICU or in-hospital stays related to the surgery with neuronavigation [15,28,29]. The average of the postoperative hospital stay described was seven days in one study [28] and one to two weeks in another [29]. Only one study compared stays related to the surgery with neuronavigation and non-neuronavigation patients [15]; no significant difference between the surgery with neuronavigation and non-neuronavigation groups for the postoperative in-ICU (surgery with neuronavigation, 1 day; non-neuronavigation, 1.1 day) and the in-hospital stay (surgery with neuronavigation, 16.9 days; non-neuronavigation, 17.2 days) [15] was found.

3.9. Processing time of neuronavigation

Four out of 28 studies described processing times of surgery with neuronavigation. One study performed preoperative MRI [13], F-FDG, PET and intraoperative ECoG. This one study found the mean time spent to process all this data together was 52 min, while total mean operation time was 212 min [26]. Other studies reported a mean operating time of 213.3 min, while the overall scan time for the acquisition of intraoperative MRI sequences was 13.9 min [27] and 14 min [20]. A study showed that the intraoperative anatomic (MRI) and diffusion (diffusion tensor imaging tractography) scans took on average 54 min and 47 min, respectively [25].

3.10. Postoperative neurological deficits

This review of 704 patients undergoing surgery with neuronavigation revealed 143 patients (20.31%) who presented

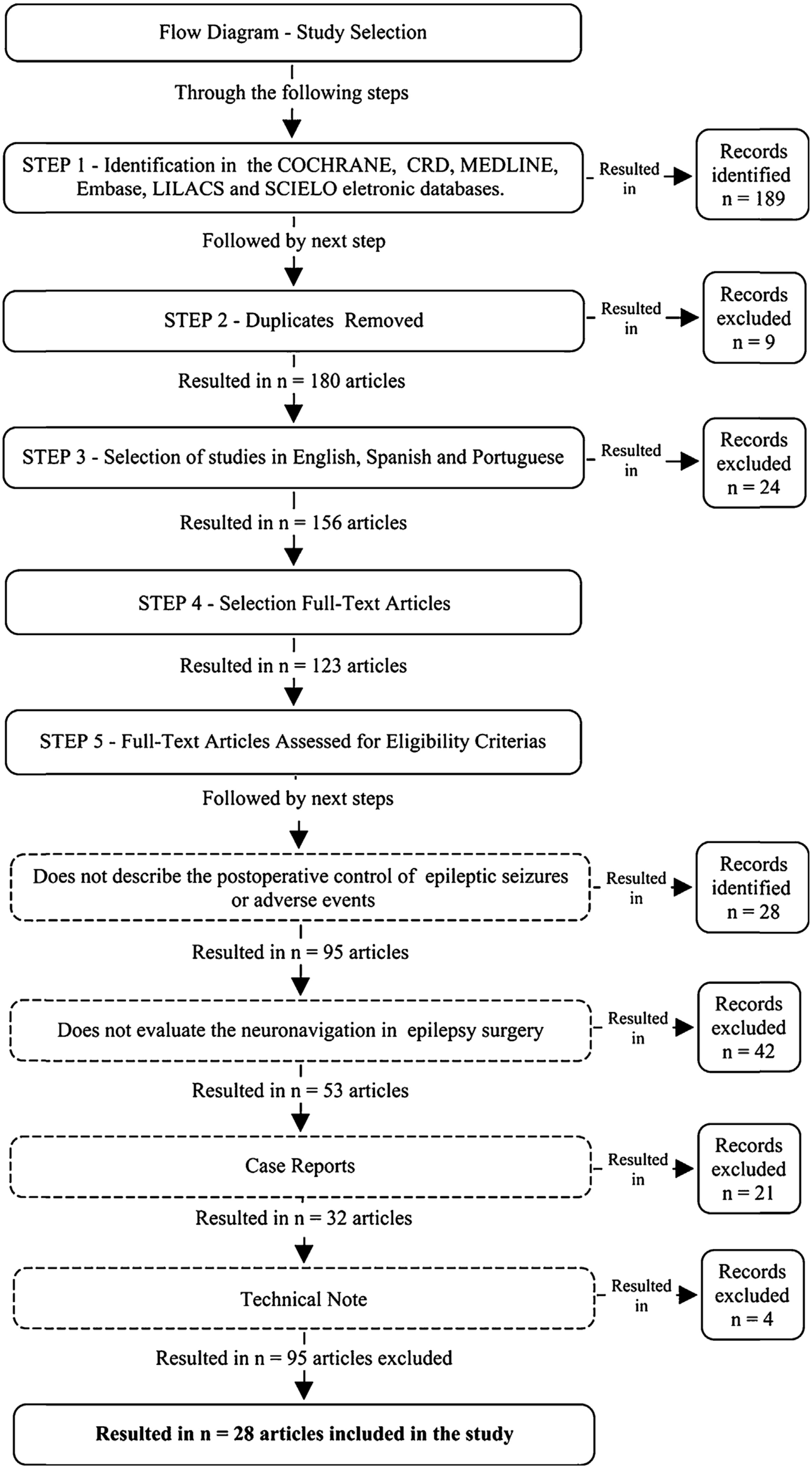

Fig. 1. Flowchart of the entire process of systematic review (A 1.5 column fitting image).

Table 1
Oxford classification and demographics of the 28 included articles.

Study (Reference #)	Oxford (GR/EL)	Number of patients	Age (mean, years)	Postsurgical follow-up time (mean, months)
Wurm et al. (2000) [28]	B/2C	16.00	35.70	19.30
Duffau et al. (2002) [35]	B/2C	11.00	35.00	24.00
Miyagi et al. (2003) [16]	B/2C	7.00	36.40	31.90
Wurm et al. (2004) [17]	B/2C	6.00	33.40	NA
Oertel et al. (2004) [15]	B/3B	37.00	33.90	28.00
Oertel et al. (2005) [19]	B/2C	30.00	35.50	25.80
Cho et al. (2005) [29]	B/2C	46.00	38.10	54.00
Iida et al. (2005) [36]	B/2C	16.00	12.00	23
Acar et al. (2008) [37]	B/2C	39.00	36.42	25.88
Park et al. (2009) [38]	B/2C	6.00	4.10	NA
Zhou et al. (2009) [39]	B/2C	6.00	33.00	NA
Levy et al. (2009) [40]	B/2C	21.00	12.00	NA
Benifla et al. (2009) [41]	B/2C	22.00	10.00	49.20
Malak et al. (2009) [42]	B/2C	9.00	29.00	59.50
Ortler et al. (2010) [24]	B/2C	25.00	37.00	NA
Spalice et al. (2010) [43]	B/2C	13.00	13.70	72.00
Kim et al. (2011) [44]	B/2C	12.00	10.90	25.70
Sun et al. (2011) [45]	B/2C	20.00	31.05	12.60
Chandra et al. (2013) [26]	B/2C	37.00	24.80	23.60
Sommer et al. (2013) [27]	B/2C	25.00	34.00	44.20
Ntsambi-eba et al. (2013) [46]	B/2C	62.00	20.30	24.00
Sommer et al. (2013) [20]	B/2C	26.00	19.90	47.70
Cui et al. (2014) [14]	B/2C	69.00	39.10	24.00
Roessler et al. (2014) [21]	B/2C	88.00	37.20	24.00
Sommer et al. (2014) [22]	B/2C	19.00	41.40	43.80
Sommer et al. (2014) [23]	B/2C	5.00	27.60	64.80
Sugano et al. (2014) [18]	B/2C	10.00	2.30	24.00
Winston et al. (2014) [25]	B/2C	21.00	36.00	NA
Mean		25.14	52.39	67.04

“Oxford”, classification of grades of recommendation (GR) and evidence level (EL) proposed by the Oxford Centre for Evidence-Based Medicine (OCEBM, 2011); NA: not available.

157 occurrences of neurological deficits, being 116 transient (73.89%) and 41 permanent deficits (26.11%) (see Table 3).

In descending order of the number of occurrences, transient neurological deficits were non-specific paresis, hemiparesis, dysphasia, cranial nerve palsy, difficulty finding the right words, visual field defects, slowness of ideation, hemotympanum, quadrantanopia, aphasia, apraxia, memory deficits, paresis of the arm, homonymous hemianopia, paresis of the leg, delirium, weakness of frontal muscle, and trigeminal hypaesthesia. Also in descending order, permanent neurological deficits were hemiparesis, visual deficits, hemianopia, decreased fine motor skills of the hand, quadrantonopsia, facial paresis, dysphasia, cognitive impairment, and cranial nerve palsy. From the non-navigation group, only described by Oertel et al., four out of 22 patients (18.8%)

Table 2
Postoperative seizure control (Engel classification).

Study (Reference #)	Patients who underwent neuronavigation					
	Patients (n)	Etiology (n free of seizures; % Engel I and II)	Engel (n/%)			
			I	II	III	IV
Wurm et al. (2000) [28]	16	TLE (16; 100%)	13	3	–	–
Duffau et al. (2002) [35]	11	Glioma (10; 91%)	9	1	1	–
Wurm et al. (2004) [17]	6	TLE (6; 100%)	6	–	–	–
Iida et al. (2005) [36]	16	TU (5; ND), MCD (4; ND), residual TU (2; ND), postexcision cavity (2; ND), Cyst (1; ND), Normal (1; ND), and Encephalomalacia (1; ND).	12	1	–	3
Acar et al. (2008) [37]	39	TLE (39; 100%)	37	2	–	–
Park et al. (2009) [38]	6	Insular Lesions (etiology not specified) (6; 100%)	5	1	–	–
Zhou et al. (2009) [39]	6	Cavernomas (6; 100%)	6	–	–	–
Benifla et al. (2009) [41]	22	Epilepsy from the Rolandic Region (18; 81.8%)	14	4	2	2
Malak et al. (2009) [42]	9	Insular Lesions (TU in 2 patients) (9; 100%)	8	1	–	–
Ortler et al. (2010) [24]	15	Cavernomas (3; 100%), TLE (7; 87.5%), Cortical Dysplasia (1; 100%), Unremarkable (1; 100%)	9	3	2	1
Spalice et al. (2010) [43]	13	TU (9; 69.2%)	3	6	4	–
Kim et al. (2011) [44]	12	FCD (8; 66.6%), Tuber (1; 8.3%), Tuber, FCD and PMG (1; 8.3%), None (1; 8.3%)	9	2	1	–
Sun et al. (2011) [45]	20	Cavernomas (19; 95.0%)	18	1	1	–
Chandra et al. (2013) [26]	37	Neocortical Lesional Epilepsies (33; 89.18%)	25	8	4	–
Sommer et al. (2013) [27]	25	ExTLE (21; 84.0%)	19	2	3	1
Sommer et al. (2013) [20]	26	Cavernomas (23; 88.4%)	21	2	2	1
Sommer et al. (2014) [22]	19	TU (19; 100%)	16	3	–	–
Sommer et al. (2014) [23]	5	Hypothalamic Harmartomas (4; 80.0%)	2	2	1	–
Total (%)	303		232/76.56%	42/13.80%	21/7.00%	8/2.64%

ND, not described; TLE, temporal lobe epilepsy; ExTLE, extratemporal epilepsy; TU, tumor; FCD, focal cortical dysplasia; PMG, polymicrogyria.

Table 3
Postoperative neurological deficits.

Postoperative neurological deficits

Neurological deficit	Wurm et al. (2000) [28]	Duffau et al. (2002) [35]	Miyagi et al. (2003) [16]	Oertel et al. (2004) [15]	Oertel et al. (2005) [19]	Cho et al. (2005) [29]	Iida et al. (2005) [36]	Acar et al. (2008) [37]	Benifla et al. (2009) [41]	Malak et al. (2009) [42]	Spalice et al. (2010) [43]
Postoperative transient neurological deficit											
Non-specific Paresis	–	–	–	–	–	–	–	–	29	–	–
Hemiparesis	–	5	–	1	1	–	1	–	10	4	–
Dysphasia	–	–	–	–	–	–	–	–	4	–	–
Difficulty Finding Right Words	–	–	–	–	–	–	–	–	4	–	
Visual Deficits	–	–	–	–	–	–	–	4	4	–	–
Hemotympanum	–	–	–	–	–	–	–	3	–	–	–
Cranial Nerve Palsy	–	–	–	1	2	–	–	2	–	–	1
Aphasia	–	–	–	1	–	–	–	1	–	–	–
Apraxia	–	–	–	–	–	–	–	–	–	–	–
Memory Deficits	–	–	–	–	–	–	–	2	–	–	–
Quadrantonopia	–	–	–	–	–	1	–	–	–	–	–
Paresis of the Leg	–	–	–	–	–	–	–	–	–	1	–
Paresis of the Arm	–	–	–	–	–	–	–	–	–	–	–
Homonymous Hemianopia	–	–	1	–	–	–	–	–	–	–	–
Slowness of Ideation	–	5	–	–	–	–	–	–	–	–	–
Delirium	–	–	1	–	–	–	–	–	–	–	–
Weakness of Frontal Muscle	–	–	1	–	–	–	–	–	–	–	–
Trigeminal Hypaesthesia	–	–	–	–	–	–	–	–	–	–	–
Subtotal	0	10	3	3	3	1	1	12	48	5	1
Postoperative permanent neurological deficits											
Hemiparesis	1	–	–	–	–	–	1	1	–	–	–
Hemianopia	–	–	–	–	–	–	–	–	–	–	–
Decrease in Fine Hand Motor Ability	–	–	–	–	–	–	–	–	–	–	–
Quadrantonopsia	–	–	–	–	–	–	–	–	–	–	–
Facial Paresis	–	–	–	–	–	–	–	–	–	–	–
Visual Deficits	–	–	–	–	–	–	–	–	–	–	–
Dysphasia	–	–	–	–	–	–	–	–	–	–	–
Cognitive Impairment	–	–	–	–	–	–	–	–	–	–	–
Cranial Nerve Palsy	–	–	–	–	–	–	–	–	–	–	–
Subtotal	1	0	0	0	0	0	1	1	0	0	0
Total											

Postoperative neurological deficits

Neurological deficit	Kim et al. (2011) [44]	Sommer et al. (2013) [27]	Ntsambi-eba et al. (2013) [46]	Sommer et al. (2013) [20]	Cui et al. (2013) [14]	Roessler et al. (2014) [21]	Sommer et al. (2014) [22]	Sommer et al. (2014) [23]	Subtotal (%)
Postoperative Transient Neurological Deficit									
Non-specific Paresis	–	–	–	–	–	–	–	–	29 (25.00)
Hemiparesis	–	–	–	–	16	–	–	–	38 (32.75)
Dysphasia	–	4	–	–	–	–	–	–	8 (7.00)
Difficulty Finding Right Words	1	–	–	–	–	–	–	–	5 (4.31)
Visual Deficits	–	–	–	–	–	1	–	–	5 (4.30)
Hemotympanum	–	–	–	–	–	–	–	–	3 (2.60)
Cranial Nerve Palsy	–	–	–	–	–	–	–	–	6 (5.17)
Aphasia	–	–	–	–	–	–	–	–	2 (1.72)
Apraxia	2	–	–	–	–	–	–	–	2 (1.72)
Memory Deficits	–	–	–	–	–	–	–	–	2 (1.72)
Quadrantonopia	–	2	–	–	–	–	–	–	3 (2.52)
Paresis of the Leg	–	–	–	–	–	–	–	–	1 (0.86)
Paresis of the Arm	–	1	–	–	–	–	–	1	2 (1.72)
Homonymous Hemianopia	–	–	–	–	–	–	–	–	2 (1.72)
Slowness of Ideation	–	–	–	–	–	–	–	–	5 (4.31)
Delirium	–	–	–	–	–	–	–	–	1 (0.86)
Weakness of Frontal Muscle	–	–	–	–	–	–	–	–	1 (0.86)
Trigeminal Hypaesthesia	–	–	–	–	–	1	–	–	1 (0.86)
Subtotal	3	7	0	0	16	2	0	1	116

Table 3 (*Continued*)

Postoperative neurological deficits

Neurological deficit	Kim et al. (2011) [44]	Sommer et al. (2013) [27]	Ntsambi-eba et al. (2013) [46]	Sommer et al. (2013) [20]	Cui et al. (2013) [14]	Roessler et al. (2014) [21]	Sommer et al. (2014) [22]	Sommer et al. (2014) [23]	Subtotal (%)
Postoperative transient neurological deficit									
Hemiparesis	3	1	1	–	10	–	–	–	18 (44.0)
Hemianopia		–	1	–	–	–	1	–	5 (12.2)
Decrease in Fine Hand Motor Ability	3	–	–	–	–	–	–	–	1 (2.43)
Quadrantonopsia	–	–	1	–	–	–	–	–	1 (2.43)
Facial Paresis	–	–	1	–	–	–	–	–	1 (2.43)
Visual Deficits	–	–	–	3	–	9	–	–	12 (29.26)
Dysphasia	–	–	–	–	–	1		–	1 (2.43)
Cognitive Impairment	–	–	–	–	–	–	1	–	1 (2.43)
Cranial Nerve Palsy	–	–	–	–	–	–	–	1	1 (2.43)
Subtotal	7	1	4	3	10	10	2	1	41
Total									157

presented postoperative neurological deficits. They were all transient, i.e., temporary hemiparesis ($n = 2$) and temporary cranial nerve palsy ($n = 2$) [15].

3.11. Postoperative clinical and surgical complications

Three deaths were reported among the studies of surgery with neuronavigation. One death was reported in a series of patients with epilepsy foci in the insular region and who underwent surgery with neuronavigation for epilepsy. The patient had anaplastic astrocytoma, achieved Engel class IA status, refused adjuvant therapy, and died three months later due to sepsis [15]. Two deaths were described in a series of adult patients with drug resistant epilepsy who had been operated on for hypothalamic harmartomas. One patient died of cardiogenic shock and multi-organ failure due to an undiagnosed cardiomyopathy and the other died of pulmonary embolism after a status epilepticus [23]. In the only study that evaluated a non-neuronavigation casuistic, no death was described [15].

4. Discussion

This is a comprehensive systematic review of studies addressing efficacy in seizure control and safety of surgery with neuronavigation for epilepsy. Twenty-eight selected studies for this review suggested good performances of surgery with neuronavigation in epilepsy. In the present review, the scarce literature regarding efficacy in seizure control and safety of the surgery with neuronavigation were compiled and discussed, and compared to conventional neurosurgery in epilepsy. As a result, articles were found with low levels of evidence or grades of recommendation for using neuronavigation for epilepsy surgery, according to the levels of evidence from the OCEBM [11]. Therefore, the exact clinical efficacy in seizure control and safety of neuronavigation for epilepsy surgery will be ensured when surgical and clinical trials have been conducted with appropriate research designs. Nevertheless, our review found surgery with neuronavigation has performances equal to or slightly higher than conventional neurosurgery for epilepsy.

A decade ago, a systematic review examined the efficacy in seizure control of conventional neurosurgery for epilepsy in 32 studies involving 2250 patients and found a rate of 65% seizure control [30]. More recently, studies showed these rates may range from 43 to 75% in different surgical series [31]. For surgery with neuronavigation, our review analyzed surgical outcomes of 303 patients reported by 18 of 28 selected studies that reported the Engel Classification of epilepsy surgery outcome [30]. A satisfactory seizure outcome (Engel class I and II) was found in 90.36% of patients who underwent surgery with neuronavigation. Including the results described by Cui et al., the rate of good seizure outcome was 82.37% [14].

Also, surgery with neuronavigation reduced the need for re-resection, as described in the five studies that addressed this issue, among the selected studies [15,20–23]. The Oertel et al.'s study found that the conventional surgery group needed 16.5% more re-resections than epilepsy surgery with neuronavigation group [15]. Oertel et al. reported that after ECoG for temporal lobe surgery, there was a need for extension of the resection in 30.6% of patients in the surgery with neuronavigation group versus 47.1% in the control group. On the other hand, 52.6% of patients in the surgery with neuronavigation group and 63.2% in the control group remained seizure free after surgery. This finding may be due to the result of the re-resection in the second group. It is well known how undesirable approaching a brain area previously operated on is. In this setting, performing ECoG or acquiring brain MRI during or immediately after the surgical approach may enable a more complete resection of lesions [29,32].

Regarding safety of surgery with neuronavigation, the rate of neurological deficits in 704 patients was 20.31%, i.e., 143 patients. From this, almost 75% of neurological deficits were of transitory duration. Neurological deficits were 17.39% for surgery with neuronavigation and 18.18% for conventional surgery in one study [15], and 7.90% surgery with neuronavigation versus 17.4% conventional surgery in another [33]. Future studies should evaluate whether intraoperative MRI, by detecting morphological changes of the brain during surgery, can save resections in eloquent areas avoiding permanent damage [33].

Regarding efficiency of surgery with neuronavigation, a comparative study showed surgical duration was slightly greater for surgery with neuronavigation than conventional surgery [15]. On average, duration of surgery with neuronavigation was 224.06 min [15,19,20,26,27], compared to 208 min for non-neuronavigation [15]. Time required for assembly, mapping and image processing ranged from 13.9 to 52.0 min [26,27]. Of course, these times may be dependent on the technology used, ease of use and image processing time.

In relation to postoperative parameters, in-ICU and in-hospital stay, there was no significant difference between techniques with and without neuronavigation. The in-ICU stay lasted around one day and the in-hospital stay was around 17 days [15]. Other studies not considered in this systematic review showed stays even shorter than those described above [34].

5. Implications for practice

The present review found the following implications for practice: (a) Surgical efficacy in seizure control of surgery with neuronavigation is quite heterogeneous, reaching values as high as the average of 90.36% found in heterogeneous observational studies, and as low as that described by Oertel et al. This author described a low efficacy in seizure control of surgery with neuronavigation (52.6%) compared with the non-neuronavigation group (63.2%). Only with well-designed studies and with larger samples, the efficacy in seizure control of surgery with neuronavigation can be better established and compared to conventional surgery; (b) Surgery with neuronavigation reduced the need for repetition of surgical resection; (c) Surgery with neuronavigation was associated with a low rate of neurological deficits, and when they occur, are with mainly transitory neurological deficits; (d) Ultimately, there is a conceptual problem regarding the location of the EZ that should be considered in future studies on neuronavigation. Some researchers argue that the seizure generation may not occur in lesional tissue but at the borders of imaging-based "normal" brain tissue [48]. From the neurosurgical point of view, this problem does not necessarily preclude the possibility of epilepsy surgery. The surgical approach may involve not only the visible lesion, but also the epileptogenic tissue suggested by ECoG and depth electrodes [47]. In particular, functional neuroimaging like positron emission computed tomography (PET) and subtraction ictal SPECT co-registered with MRI (SISCOM) can assist in the placement of invasive EEG. On the other hand, functional magnetic resonance (fMRI) can help to spare non-epileptogenic cortex around the lesion from resection.

6. Implications for research

Future studies should be conducted with a high level of evidence and grades of recommendation to ensure the greatest efficacy in seizure control and effectiveness of surgery with neuronavigation versus conventional surgery in epilepsy. Also, future studies should evaluate the efficacy in seizure control and safety of surgery with neuronavigation upon parameters such as classifications of epilepsy syndromes and seizures, brain areas operated, the nature of the lesions found, and postoperative follow-up.

7. Limitations

Possible limitations of this study can be: (a) The small number of final selected studies; (b) The research design of the majority of selected studies on neuronavigation and epilepsy surgery were not adequate to answer whether neuronavigation provides advantages regarding efficacy and safety of epilepsy surgery; (c) The term neuronavigation was first used in 1993 and was included in the library of medical vocabularies, MeSH, PubMed, only in 2003; (d) Delay for the acceptance of the term "neuronavigation" by the medical, scientific and business communities; (e) The rapid development and the large volume of new technologies is not accompanied by adequate study and evaluation of new technologies in health.

8. Conclusions

This systematic review found studies with a low evidence level and low grade of recommendation, in a mix of newer and older studies, by applying different neuronavigation technologies. We were unable to find any publications providing convincing evidence that neuronavigation improves outcomes of epilepsy surgery. Whilst this does not mean that neuronavigation cannot improve neurosurgical outcomes in this clinical setting, well-designed research studies evaluating the role of neuronavigation are urgently needed.

Conflicts of interest statement

The authors report no conflicts of interest.

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