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REVIEW

Early surgical approaches in pediatric epilepsy — a systematic review and meta-analysis

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Abstract

Introduction Drug-resistant epilepsy occurs in up to 30% of children suffering from seizures and about 10% qualify for surgical treatment. The aim of this systematic review and meta-analysis is to analyze the potential benefit of early epilepsy surgery in children concerning primarily seizure and developmental outcome.

Methods PubMed and Embase databases were searched using a systematic search strategy to identify studies on pediatric epilepsy surgery under 3 years from their inception up to 2022. Outcome measures were seizure outcome, postoperative complications, seizure onset, and reduction rate of antiepileptic drugs. A meta-analysis was thereafter performed for all included cohort studies. A p-value of <0.05 was considered as statistically significant.

Results A total of 532 patients were analyzed with 401 patients (75%) receiving resective or disconnective surgery under the age of 3 years and 80 patients (15%) receiving surgery older than 3 years. The remaining 51 patients (9%) underwent VNS implantation. Pooled outcome analysis for resective/disconnective surgery showed favorable outcome in 68% (95% CI [0.63; 0.73]), while comparative analysis between the age groups showed no significant difference (77% early group and 75% late group; RR 1.03, 95% CI [0.73; 1.46] $p=0.75$). Favorable outcome for the VNS cohort was seen in 52%, 65% in the early and 45.1% in the late group (RR 1.4393, 95% CI [0.87; 2.4] $z=1.42$, $p=0.16$). Developmental outcome was improved in 26%. Morbidity rate was moderate and showed no significant difference comparing the age groups, and overall surgical mortality rate was very low (0.1%).

Conclusion Epilepsy surgery in pediatric age, especially under the age of 3 years, is a feasible and safe way to treat intractable epilepsy. Further comparative studies of prospective nature, analyzing not only seizure but also developmental outcome, should be the focus of future studies.

Keywords Pediatric epilepsy surgery · Intractable epilepsy · Drug-resistant epilepsy · Pediatric neurosurgery

Abbreviations

AED	Antiepileptic drug
VNS	Vagus nerve stimulation
DBS	Deep brain stimulation
RNS	Responsive neurostimulation
TS	Tuberous sclerosis
EC	Encephalitis
I	Idiopathic
HME	Hemimegaencephalie
CD	Cortical dysplasia
SWS	Sturge-Weber syndrome
VM	Vascular malformation
LEAT	Low-grade epilepsy associated tumors
IS	Ischemic stroke
HM	Hippocampal malformation
IVH	Intraventricular hemorrhage
SY	Syndromes
CP	Cerebral palsy
NA	No detailed information available
HO	Hemispherotomy
HE	Hemispherectomy
LO	Lobectomy
LE	Lesionectomy
MLD	Multilobar disconnection
DQ	Developmental quotient

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Introduction

In pediatric patients, seizure can occur at any age and has a devastating impact on cognitive development and quality of life [1]. Even after a short duration of uncontrolled seizures, morbidity is significantly increased [2]. About a third of this pediatric population does not respond to antiepileptic drug medication (AED) and traditionally, about 10% qualify for epilepsy surgery [3]. Over the last decades, the advances in epilepsy surgery, including resective procedures and modulating surgical approaches, led to an increase in usage, with mostly positive results [4]. Indications for epilepsy surgery in case of intractable epilepsy are hemimegalencephaly (HME), cortical dysplasia (CD), tuberous sclerosis (TS), vascular lesions, Sturge-Weber syndrome (SWS) or tumors, and ischemic pathologies. For clearly demarcated epileptogenic lesions, resective surgery with uni- or multilobar lesionectomy is recommended, while for anatomically widespread lesions or electrophysiologically not completely allocated epileptogenic foci, functional or anatomical disconnecting procedures as well as lobectomies are warranted [5]. Neurostimulative procedures such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) are usually used as alternative surgical approaches in case of widespread epileptogenic foci that are often not amendable for resective or disconnective surgery [6–9]. Randomized controlled trials (RCTs) in adult cohorts proved benefit and favorable outcome with DBS, VNS, and RNS, but there is a lack of RCT and prospective trials for pediatric cohort [7].

In the literature, no consensus exists about the optimal timing for epilepsy surgery in children with drug-resistant epilepsy (DRE). However, some reports suggest that early epilepsy surgery leads to better response with improved cognitive outcome and better seizure control [10]. In addition, the risk profile for surgical procedures in younger children is different than in older patients, due to the more friable tissue in infants and higher risk for blood transfusion [11].

The aim of this systematic review and meta-analysis is to analyze the potential benefit of early epilepsy surgery in children concerning primarily seizure and developmental outcome.

Methods

For this systematic review, two databases (PubMed and Embase) were systematically searched and reports published in English from the inception of the databases until January 2022 were included. Our systematic search string included a combination of the terms "epilepsy surgery" and "pediatric" and "early."

For resective surgery, "early" was defined as surgery ≤ the age of 3 years, since most of the reviewed literature suggested this age cutoff. For VNS treatment, "early" was defined ≤ the age 5 of years since most comparative studies set the limit for early treatment at this age. We included randomized trials (RCT), prospective and retrospective cohort studies, comparing early and late surgical treatment of epilepsy, as well as descriptive case series including more than 5 pediatric patients receiving early epilepsy surgery. Technical reports, case reports, comments, editorial letters, poster abstracts, and reviews were excluded from this review.

Removal of duplicates and screening of the results were carried out with the help of the web-based software Rayyan [12]. Initially, two authors (N.F. and L.G.) independently screened the reports according to their title and then their abstract. Thereafter, a final list was compiled which underwent full-text review, while the reference list of included articles was screened as well (other sources). In case of disagreement concerning the in- or exclusion of an article, the senior author (J.S.) took the final decision.

We extracted the following information from eligible reports: study details (author, year of publication, design); study population (number of participants, median/mean age, mean/median follow-up); treatment characteristics (pathology, interval of seizure onset to surgical treatment, type of surgery); and outcome measures (seizure outcome, developmental outcome).

Primary outcome was favorable seizure outcome defined as Engel I and II [13] or ILAE score of 1 or 2 [14]. Secondary outcomes were developmental outcome, reduction of antiseizure medication, morbidity, and mortality. Total number of patients of each study and subgroup distribution was documented as well. If datasets for analysis were missing, a note "NA" was placed in the according table (Tables 1, 2, and 3). Since some included reports were composed of data for children under and above 3 years of age, we collected the data of these reports to analyze the primary and secondary outcome and to compare them to the results of the target group.

Qualitative assessment

Quality assessment of the retrospective cohort studies was carried out using the Newcastle–Ottawa scale (NOS) [15] and was initially conducted by two authors independently (N.F., L.G.) and then compared.

Statistical analysis

Risk ratio (RR) was used as an effect measure for the pooled outcomes. Depending on the heterogeneity ($I^2 < 50\%$) of the

Table 1 Distribution of pathologies among age groups and surgical/functional group

Age	HME	TS	CD	SWS	LEAT/tumor	HM	IS	EC	VS	SY	IVH	CP	I	NA
< 3 yrs	66	60	117	25	44	10	20	11	2	5	2	0	0	38
> 3 yrs	2	9	16	0	21	11	1	3	0	0	1	0	0	17
Total	**68**	**69**	**133**	**25**	**65**	**21**	**21**	**14**	**2**	**5**	**3**	**0**	**0**	**55**
VNS														
< 3 yrs	1	1	0	0	0	0	1	3	0	4	2	3	7	0
> 3 yrs	0	0	0	0	0	0	0	4	0	2	1	2	20	0
Total	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**7**	**0**	**6**	**3**	**5**	**27**	0

EC encephalitis, *I* idiopathic, *HME* hemimegaencephalie, *CD* cortical dysplasia, *SWS* Sturge-Weber syndrome, *VS* vascular malformation, *TS* tuberous sclerosis, *LEAT* low-grade epilepsy associated tumors, *IS* ischemic stroke, *HM* hippocampal malformation, *IVH* intraventricular hemorrhage, *SY* syndromal, *CP* cerebral palsy, *NA* not applicable

studies, either the fixed-effect or random-effects model was applied. Forest plots were generated for primary outcome. All analyses were done using the R statistical software (version 4.0.3, 2020) with the help of the dmetar package [16]. A p-value of < 0.05 was considered as statistically significant. No sensitivity analysis ("leave one out method") was performed due to the limited number of comparative studies.

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).

Results

We initially identified 1038 reports. After title screening, 70 report abstracts were further assessed. Of these, 49 articles underwent full-text evaluation whereof 12 articles were included in qualitative analysis, and two reports were added through screening of references (Fig. 1) leading to a cohort of 532 patients. Ten reports (481 patients) analyzed the outcome of early resective or disconnective epilepsy surgery [11, 17–25]. Of these, four reports (80 patients) compared the outcome to late epilepsy surgery [20–22, 24]. Early VNS surgery was analyzed in 2 reports (51 patients). One report analyzed the outcome after early VNS surgery (6 patients), while one report compared the outcome of early (14 patients) and late (31 patients) VNS surgery [22]. All included reports were of retrospective nature. Mean NOS was 6.25 points (± 0.25).

Comparison of early and late epilepsy surgery

Of the included 532 patients, 401 (75%) received early epilepsy surgery. The distribution of treated diseases within the whole cohort and for the early and late group is presented in Table 1 showing a rather heterogeneous distribution. The early surgery group presented with more hemispheric, widespread lesions or syndromic pathologies, whereas the late surgery group presents with more depicted lesions such as tumors in relation to cohort size.

Age distribution at surgery was available for all studies. Mean age at surgery of the cohort was 25.7 months (95% CI [4.6; 46.7], range 72 days and 107 months), while the mean age of the early group was 14.2 months (95% CI [10.1; 18.4], range 2.4–20.0 months) and of the late group was 66.0 months (95% CI [53.0; 84.5], range 49.6–107.0 months). Jenny et al. did not declare an age distribution in their cohort [21]. Mean age at seizure onset was 2.9 months (95% CI [0.7; 5.3], range 6 days to 24 months) and 0.6 months for the early group and 10.1 months for the late group ($p = 0.03$).

The distribution of the surgical approach for the whole cohort and the early and late group is presented in Table 2. One report did not present detailed information on surgical technique [22].

Overall favorable outcome was 0.68 (95% CI [0.63; 0.73]) (Fig. 2a). Favorable outcome was comparable in both groups with 77% in the < 3 years group and 75% in the > 3 years group with a higher rate of seizure-free outcome of 91% ($n = 270$) in the < 3 years group and 88% ($n = 70$) in the > 3 years group.

Table 2 Distribution of surgical procedures among age groups

Age	HE	HO	MLD	LO	LE	VNS
< 3 yrs	64	104	24	36	137	14
> 3 yrs	5	10	1	24	29	31
Total	69	124	25	60	166	45

HO hemispherotomy, *HE* hemispherectomy, *LO* lobectomy, *LE* lesionectomy, *MLD* multilobar disconnection, *VNS* vagus nerve stimulation

Table 3 Descriptive trials of early epilepsy surgery

Author	*n* (total)	*n* < 3 years	*n* > 3 years	Etiology < 3 yrs | > 3 yrs	Surgical approach < 3 yrs | > 3 yrs	Age at surgery months (mean; (SD))	Age at surgery months < 3 years (mean; (SD))
Iwasaki et al. 2021 [17]	75	75	NA	HME (22); CD (33); LEAT (10); TS (6); SWS (3); IS (1)	HO (27); MLD (19); LO (13); LE (16)	11.9 (±10.8)	11.9 (±10.8)
Roth et al. 2021 [11]	64	64	NA	CD (28); HME (5); TS (5); SWS (1); LEAT (1); IS (1); NA (4)	HO (37); HE (10); LE (12); LO (7); NA (1)	2.4 (±0.73)	2.4 (±0.73)
Kadish et al. 2018 [19]	48	48	NA	CD (9); HME (7); IS (6); LEAT (4); TS (4); HM (9); NA (9)	HO (22); LE (26) (8 multilobar)	18 (±9)	18 (±9)
Grayson et al. 2020 [18]	19	19	NA	(19) TS	LE (17); LO (4)	16.9 (±4.4)	16.9 (±4.4)
Steinbok et al. 2009 [25]	116	116	NA	CD (35), SWS (19), LEAT (22), HME (13), TS (9), IS (8), VM (2), Aicardi syndrome (1), EC (6), Walker-Warburg syndrome + CD + tumor (1)	HE (40); LO (7); LE (35)	15.8 (±8.5)	15.8
Ramantani et al. 2013 [23]	30	30	NA	HME (6), Aicaridi syndrome (1), CD (21), IS (3), LEAT (3)	HO (14); LE (16)	20 (±7.15)	20 (±7.15)
Villarejo et al. 2013 [22]	17	6	11	(1) EC; (2) HME; (3) CD | (2) EC; (9) CD + Vasc	NA | NA	70.8	17.6 (±9)
Lettori et al. 2008 [24]	19	14	5	(9) HME; (1) SWS; (5) NA | (1) EC; (1) IS; (2) HME; (1) IVH	HE (14) | HE (5)	27.4 (±20.2)	14.4 (±11.5)
Fohlen et al. 2018 [20]	15	10	5	(10) TS | 5 (TS)	MLD (3); LE (7) | LE (5)	25 (±20.1)	12.4 (±8.51)
Jenny et al. 2016 [21]	78	19	59	(3) TS; (1) SWS; (7) CD; (2) HME; (1) IS; (1) HM; (4) LEAT | (8) NA; (3) TS; (5) IS; (11) HM; (7) CD; (4) EC; (21) LEAT	MLD (2); HO (4); LO (5); LE (8) | LO (24); HO (10); LE (24); MLD (1)	98 (±60)	NA
Total	481	401	80	481	464	25.7 (±29.9)	14.2 (±5.2)

Table 3 (continued)

Author	Age at surgery months > 3 years (mean; (SD))	Age at seizure onset months (mean; (SD))	Age at seizure onset months < 3 years (mean; (SD))	Age at seizure onset months > 3 years (mean; (SD))	Seizure duration months (mean; (SD))	AED reduction rate mean (± SD) total	AED reduction rate mean < 3 years (± SD)
Iwasaki et al. 2021 [17]	NA	3.6 (± 6.2)	3.6 (± 6.2)	NA	8.3 (± 7.9)	0.89 (± 1.25)	0.89 (± 1.25)
Roth et al. 2021 [11]	NA	0.22 (± 0.39)	0.22 (± 0.39)	NA	NA	2 (± 0.5)	2 (± 0.5)
Kadish et al. 2018 [19]	NA	5 (± 6)	5 (± 6)	NA	13 (± 8)	NA (18 off medication)	NA
Grayson et al. 2020 [18]	NA	3.4 (± 2.6)	3.4 (± 2.6)	NA	10.5 (± 4.15)	NA	NA
Steinbok et al. 2009 [25]	NA	0–24 mo	0–24 mo	NA	NA	NA (45 off medication)	NA
Ramantani et al. 2013 [23]	NA	5 (± 5)	5 (± 5)	NA	15.7	NA (13 out of medication, 7 reduced)	NA
Villarejo et al. 2013 [22]	107.1 (± 50.9)	20.41 (± 32.92)	4.83 (± 9.3)	33 (± 38.4)	69	0.76 (± 1.03)	0.5 (± 0.83)
Lettori et al. 2008 [24]	49.8 (± 9)	2.9 (± 7.23)	0.89 (± 1.15	6.49 (± 11.45)	NA	NA (5 out of medication, median 1 remaining)	
Fohlen et al. 2018 [20]	49.6 (± 10.5)	0.45 (± 0.53	0.41 (± 0.57)	0.51 (± 0.5)	NA	NA (n4 off medication)	NA
Jenny et al. 2016 [21]	NA	NA	NA	NA	NA	1.2 (n25 off medication)	1.22
Total	66 (± 33.14)	2.9 (± 5.3)	0.6 (± 6.4)	10.1 (± 17.29)		1.21 (± 0.55); 110/481 off medication	1.15 (± 0.63)

Table 3 (continued)

Author	AED reduction rate mean > 3 years (± SD)	Favorable outcome Engel I/II (ILAE 1;2) < 3 yrs |> 3 yrs	Seizure free Engel Ia < 3 yrs |> 3 yrs	Developmental improvement	Morbidity (*n*) < 3 yrs |> 3 yrs || total	Surgical mortality (*n*)	NOS
Iwasaki et al. 2021 [17]	NA	(63) | NA	(62) | NA	Improvement	19	0	6
Roth et al. 2021 [11]	NA	(43) | NA	(42) | NA	NA	13 (hydro), total 31	0	6
Kadish et al. 2018 [19]	NA	40 | NA	29 | NA	6 improvements; 27 no change, 13 decline	10	0	6
Grayson et al. 2020 [18]	NA	12 | NA	10 | NA	No sig. change	11	0	5
Steinbok et al. 2009 [25]	NA	87 | NA	72 | NA	64 improved	54 (151 OP)	1	6
Ramantani et al. 2013 [23]	NA	24 | NA	21 | NA	26 improved, 2 stagnations (only 28 with preOP evaluation)	5	0	6
Villarejo et al. 2013 [22]	0.9 (± 1.1)	3 | 7	2 | 5	No sig. change	NA	NA	6
Lettori et al. 2008 [24]		13 | 6	9 | 4	10 improved, 4 unchanged	10 (including mild/transient)	0	7
Fohlen et al. 2018 [20]	NA	9 | 4	6 | 1	Improvement	0	0	7
Jenny et al. 2016 [21]	1	17 | 43	17 | 43	NA	3	0	7
Total	0.95 (± 0.07)	311/401 (77%) | 60/80 (75%)	270/311 (91%) | 53/80 (88%)	106/401 (26.4%) improvement; 33/401 (8.2) stable	137/401 (34.1%) | 5/80 (6.25%) || 142/481 (29%)	1/401 (0.2%)	6.25 (± 0.6)

EC encephalitis, *I* idiopathic, *HME* hemimegaencephalie, *CD* cortical dysplasia, *SWS* Sturge-Weber syndrome, *VM* vascular malformation, *TS* tuberous sclerosis, *LEAT* low-grade epilepsy associated tumors, *IS* ischemic stroke, *HM* hippocampal malformation, *IVH* intraventricular hemorrhage, *LGS* Lennox-Gastaut syndrome, *WS* West syndrome, *CP* cerebral palsy, *HO* hemispherotomy, *HE* hemispherectomy, *LO* lobectomy, *LE* lesionectomy, *MLD* multilobar disconnection, *DQ* developmental quotient, *NA* no detailed information available

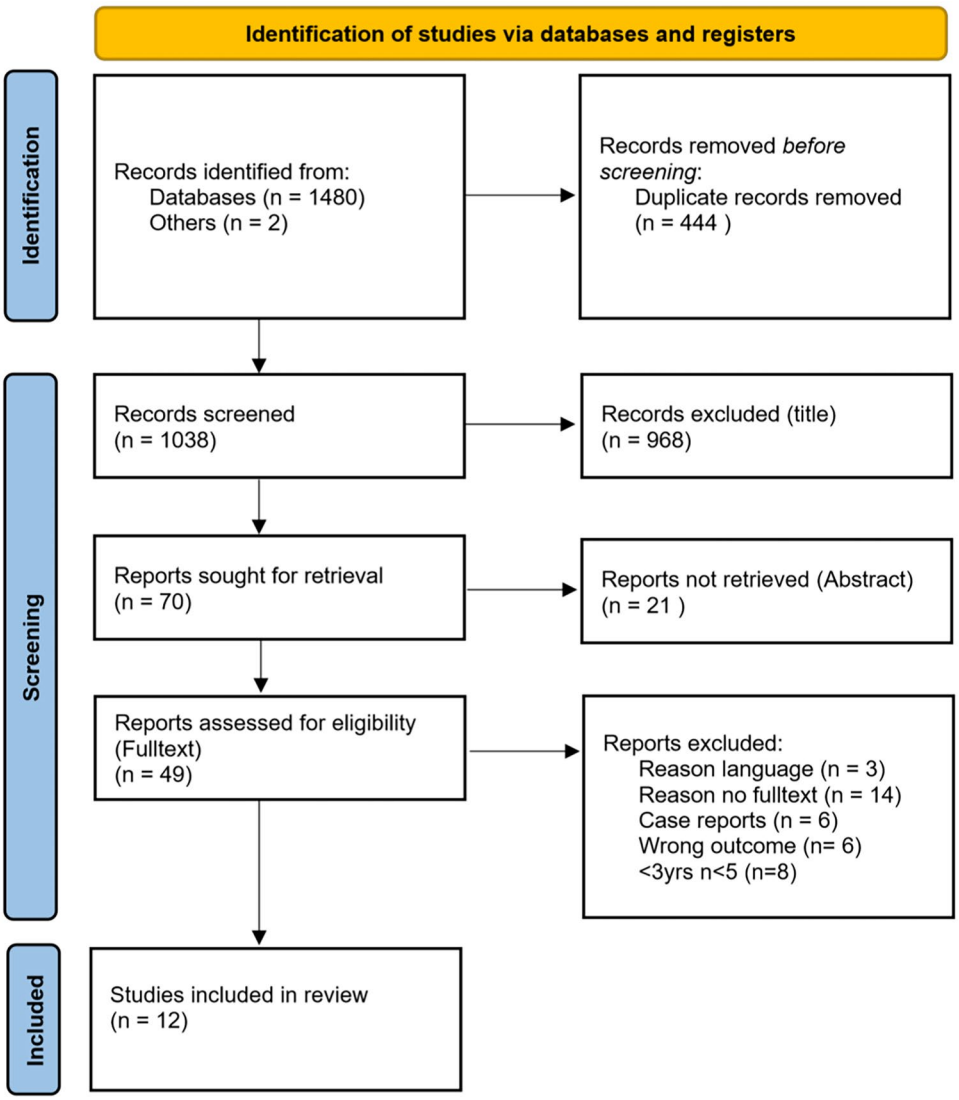

Fig. 1 Flow chart according to PRISMA guidelines for systematic review and meta-analysis

There was no significant difference in the outcome analyzing the comparative studies only (RR 1.03, 95% CI [0.73; 1.46] $p = 0.75$) (Fig. 2b).

Reduction rate of AED after epilepsy surgery of the whole cohort was mean 1.21 drugs (±0.55) based on 4 studies [11, 17, 21, 22], while 22% (110/481) of the patients were off medication during follow-up. Reduction rate of AED for the early group was 1.15 (±0.63) compared to 0.95 (±0.07) in the late group.

Information about developmental outcome was described in 8 reports [17–19, 22–25]. Out of these, 106 patients showed an improvement (26.4%), while 33 patients (8.2%) remained stable. Comparison of developmental outcome between the groups was not possible due to the lack of details and consistency within the reports. Overall morbidity was seen in 29.5% ($n = 142$), while morbidity rate in the early group was 34.1% ($n = 137$) compared to 6.25% in the late group ($n = 5$; RR 5.4 95% CI [2.3; 12.9] $p < 0.001$) [11, 17–21, 23–25]. No significant difference between the groups was detected analyzing the comparative studies only (RR 0.8, 95% CI [0.3; 2.4] $z = -0.24$, $p = 0.8$, Fig. 2c). Surgical mortality occurred in 1 patient within the early group (Table 2).

Comparison of early and late VNS surgery

VNS stimulator was implanted in 51 patients, 20 (39.2%) early and 31 (60.8%) late. None of the reports describing disconnective or resective procedures presented VNS implantation or other neuromodulative approaches in their cohorts. The mean age at surgery was 76 months (±81), 28 (±11.6) in the early group and 177.7 (±208.5) months in the late group. The underlying pathology of the whole group and the early and late group is presented in Table 1. Favorable outcome was seen in 52% ($n = 27$) of the patients, 65% ($n = 13$) in the early and 45.1% ($n = 14$) in the late group

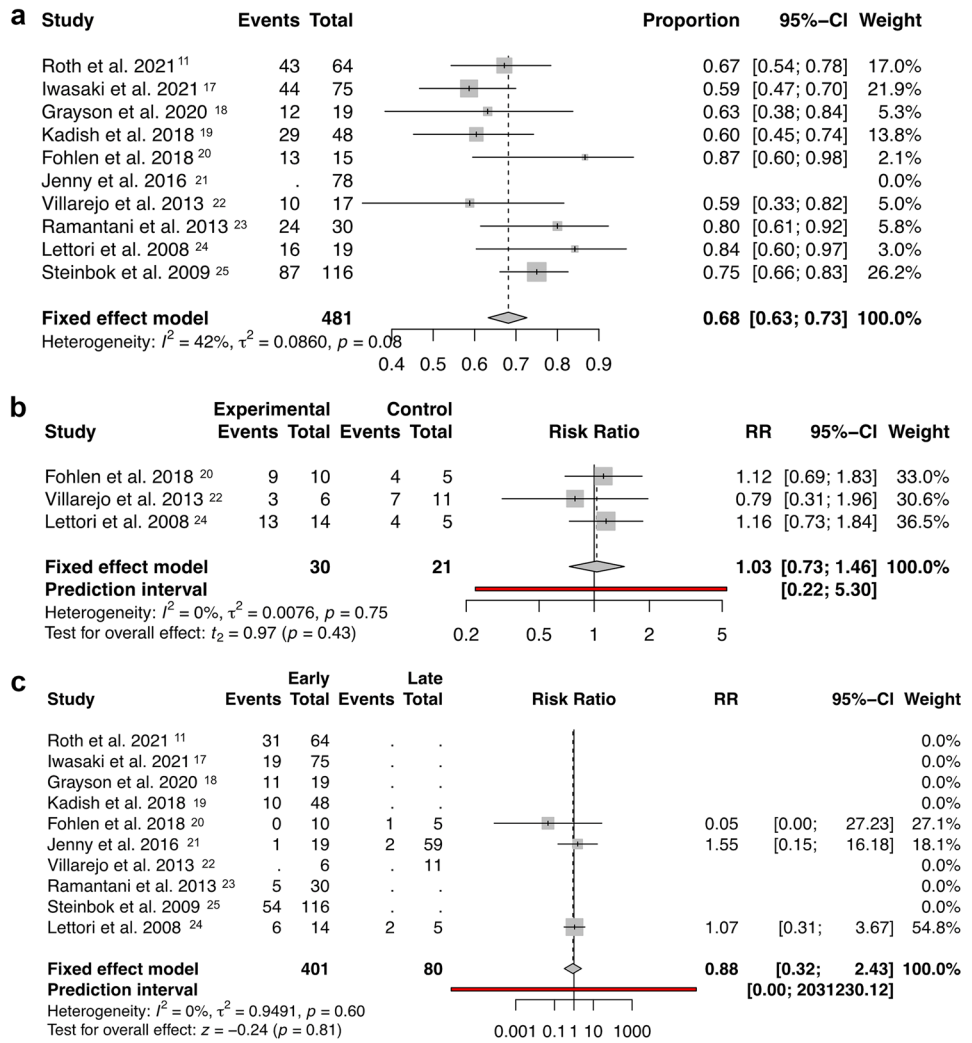

Fig. 2 **a** Pooled analysis of the overall outcome after epilepsy surgery from the surgical cohort. Overall favorable outcome was 68%. **b** Forest plot of the comparative studies for favorable outcome. No significant difference was detected ($p = 0.75$). **c** Forest plot assessing the morbidity rate of the comparative studies showing no significant difference between the age groups

(RR 1.4393, 95% CI [0.87; 2.4] $z = 1.42$, $p = 0.16$). Improved developmental outcome was seen in 27% of the patients, in the cohort of Soleman et al. with significance for the early treatment group [26]. No mortality occurred and complication rate was 28% ($n = 13$), 21% ($n = 3$), and 32% ($n = 10$) for the whole cohort, the early, and the late group, respectively (Table 4).

Discussion

To our knowledge, this is the first systematic review and meta-analysis regarding early epilepsy surgery in children with focus of young children under 3 years of age. We identified a total of 12 articles with a total of 532 patients, 481 undergoing resective surgery and 51 undergoing VNS implantation.

Hemispherotomy was the most common used surgical approach in children < 3 years, while children > 3 years were mostly treated with lesionectomies. Favorable outcome was comparable in both groups with 77% in the < 3 years group and 75% in the > 3 years group. Seizure freedom was more frequently in the < 3 years group. Overall morbidity rate was 29%, while 34% of the early group suffered complications such as the need for blood transfusion, hypothermia, and hydrocephalus. This difference is probably due to the higher amount of hemispheric surgical approaches in the early group. Developmental improvement was seen in 26.4% of all patients. Overall surgical mortality rate was very low at 0.2%. Two of the included studies described the outcome of VNS treatment, which has a lower rate of favorable outcome (52%), with a higher rate of favorable outcome in the early treatment group (65%) than in the late treatment group (45%) but a higher described developmental improvement in the < 3 years cohort. Overall, morbidity rate was 25% ($n = 133$), a distinction between the age group was not possible due to missing baseline data. Mean reduction rate of AED after surgery was 1.21 drugs and 22% of the surgical patients came off medication.

Table 4 Functional surgery

Author	*n* (total)	*n* < 3 years	*n* > 3 years	Age at surgery months (mean; (SD))	Age at surgery months (mean; (SD)) < 3 years	Age at surgery months (mean; (SD)) > 3 years	Age at seizure onset months (mean; (SD))	Age at seizure onset months (mean; (SD)) < 3 years	Age at seizure onset months (mean; (SD)) > 3 years	Seizure duration months (mean; (SD))	Favorable outcome Engel I/II early | late || total	Seizure free Engel Ia	Developmental improvement	Morbidity early | late | total	Surgical mortality	NOS
Soleman et al. 2012 [26]	45	14	31	133.9 (± 184)	37 (± 17.7)	177 (± 208)	18.4 (± 31.7)	5.4 (± 12.5)	24.5 (± 36)	NA	9 | 14 || 23	NA	Improvement in early group compared to late group	3 | 10 | 13	0	5
Zamponi et al. 2008 [31]	6	6	0	17.2 (± 6.7)	17.2 (± 6.7)	NA	4 (± 3.4)	4 (± 3.4)	NA	NA	4	1	5 improved	NA	0	5
Total	51	20	31	76 (± 81)	27.1 (± 14)	177 (± 208)	11.2 (± 10)	4.7 (± 0.9)	24.5 (± 36)	NA	27 (52%) total; 13 (65%) early	1	Improvement	3 | 10 | 13	0	5

NA not applicable

Etiology and outcome

To date, studies focusing on the surgical and developmental outcome after early epilepsy surgery in children are solely of descriptive nature, while only few retrospective studies comparing early and late epilepsy surgery exist. It is assumed that early surgery in children leads to better seizure and developmental outcome in comparison to late surgery [17]. The developing brain provides greater neuroplasticity, which gives better chances for recovery and therefore compensating transient deficits after resective surgery than in older patients [10]. However, apart from age, factors such as time to surgery, the underlying disease, and seizure semiology seem to influence outcome as well [22]. Vascular CD followed by children with vascular pathologies leading to epilepsy show worst epilepsy outcome after surgical treatment that other pathologies [22]. This is partly due to the fact that patients with vascular CD or vascular lesions are prone to severe developmental delays due to structural abnormalities of the disease itself. Therefore, for these pathologies, epilepsy surgery should be discussed at an early phase of the disease, with the aim to reduce the progression of the disease itself. In our pooled outcome analysis, CD ($n = 117$) was the most common etiology followed by HME ($n = 66$) in children < 3 years, while in older children, the most common etiology was LEAT ($n = 21$). When analyzing the type of surgical approach in relation to the different etiologies, a greater number of hemispherotomies and hemispherectomies were performed for widespread lesions and were more common in the group < 3 years. However, we did not detect any bias due to a higher number of published articles reporting about these procedures in younger children [27]. This leads to the suggestion that younger children suffer mostly from congenital or genetic pathologies whereas tumor lesions mostly predispose for epilepsy in children older than 3 years. When regarding the distribution of applied surgical procedures, lesionectomy or lobectomy was in relation to treated patients mostly used in children over 3 years.

Timing of seizure onset was early with 0.6 months in the < 3 years cohort and 10.1 months in the > 3 years cohort. The interval of seizure before surgery could not be assessed due to missing baseline data. Some studies showed that shorter seizure duration before surgery is associated with better seizure and developmental outcome [27]. Ramatani et al. found in their work that developmental impairment is less severe with a shorter duration of epilepsy [23]. Iwasaki et al. postulated to evaluate surgery even in patients that are diagnosed with an appropriate pathology, such as HME, CD, TS, or SWS before DRE is diagnosed. Existing reviews postulate a shorter interval between seizure onset and surgery to be important for favorable outcome for all age groups including adult patients but no subgroup description for very young children was made [27]. Therefore, it would be interesting

to investigate if the outcome varies in young children under 3 years, depending on the time interval between onset and surgery and age of surgery; however, the available data was too heterogeneous; therefore, this question cannot be decisively answered by our cohort of patients.

Developmental outcome showed an overall improvement in 31% of all cases. Distribution between the age groups was not possible. Previous studies suggested that a high frequency of seizures during infancy causes severe structural damage to the developing brain and therefore results in severe cognitive deterioration [1]. Furthermore, early onset and longer duration of epilepsy is directly correlated with preoperative cognitive development and therefore influences the cognitive outcome after surgery as well [1, 19, 23, 25]. Clearly, the underlying seizure pathology affects developmental outcome after seizure surgery. Focal and well-defined lesions show better developmental outcomes than hemispheric pathologies or genetic diseases leading to epilepsy [25].

The possibility to discontinue or reduce AED after successful surgery also shows beneficial effect on postoperative development [28, 29]. In our analysis, 110 patients came off medication after resective or disconnective procedures [19–21, 23–25]. A previous retrospective analysis revealed that rapid reduction or discontinuation of AED does not lead to higher seizure relapse [30]. Therefore, developmental outcome could be improved in faster reduction of AED after surgery.

Morbidity and mortality

Despite the high percentage of favorable outcomes reported and low complication rate, epilepsy surgery in young children is challenging and should not be underestimated [11, 21]. Especially in infants, the cortex is more friable, and due to the small circulating blood volume, the high rate of blood transfusion and risk of coagulopathy cannot be underestimated [11]. Roth et al. who focused on surgery in infants (< 3 months) had the highest rate of administered blood products with 96%. However, also in other studies including older children, a transfusion rate of 87% was reported [23]. The high rate of administered blood products is probably not only due to small circulating blood volume but also due to the fact that in younger children, hemispherotomies are more common that in older children, where lesionectomies are the most frequent surgery [11]. Roth et al. could show that preoperative EEG activity correlated with the need for more intra- and postoperative blood productive administration [11].

Apart from hemorrhage, other reported complications were hydrocephalus, infection, and transient hemiparesis [11, 17–26]. Some studies showed that hydrocephalus occurred significantly more often in hemispheric rather than focal surgeries [11, 19], ranging from 5.8 to 25% [11, 17, 19, 23]. Younger age predisposes for hydrocephalus complication due to the large exposure of the lateral ventricle in hemispherectomies that are more often required in the young cohort [17]. Bleeding complication more often occurs in large hemispherical surgeries such as hemispherectomies [17, 24, 25]. Complications were reported heterogeneously amongst the publications, which makes a uniform analysis difficult; nevertheless, no significant difference between the two age groups regarding complication rates and severity was described which led to the conclusion that epilepsy surgery even in young children seems safe and feasible.

VNS

VNS is mostly indicated in patients with catastrophic epilepsy as a palliative treatment. The patients often suffer from global cerebral pathologies such as encephalitis or intraventricular hemorrhage of prematurity [26, 31]. To our knowledge, there is no existing review literature focusing on neuromodulative treatment for DRE in very young pediatric patients under the specific age cutoff of 3, respectively 5 years since this approach is rather new and constantly developing [4, 7, 8]. VNS could achieve a seizure reduction in 41.8–66%. The outcome of VNS is inferior to disconnective or resective surgery, however, given that the patient collective is different with more widespread pathologies for VNS. Complication rate of VNS was reported to be rather low with an infection rate of 6.7% and disconnection of the electrodes in 2.2% without causing any permanent morbidity [26, 31]. Hence, VNS is a relatively effective, low-risk treatment option for catastrophic epilepsy even in young children.

DBS is an approved method for treatment of DRE in adults as palliative treatment with high rates of favorable outcome. A systematic review focusing on neuromodulative treatment options with DBS and VNS reported successful results for pediatric patients of all age groups suffering from DRE with moderate complication rates [7]. Neuromodulation seems to be a promising way of alternative seizure treatment with good outcomes and acceptable complication profile [7, 8, 26]. Therefore, neuromodulation should be taken into account when evaluating surgical treatment steps in cases of DRE and not only as a palliative option.

Limitations

Despite conducting a systematic review and meta-analysis, several limitations are present in this study. First, we only searched two databases (PubMed and Embase) and only

searched for English literature, which carries a risk of omitting important data published elsewhere. Second, for the quantitative meta-analysis, data were very heterogenous and only retrospective cohort studies could be included. Especially the tailored search limited the number of patients for the comparative group. Although the quality of the studies according to the Newcastle–Ottawa scale was overall fair-good, the small number of studies and the small number of patients and heterogeneity of data within the studies possibly limit the results. Especially, the number for neuromodulative treatment remained low in our search. Third, different descriptions and classifications of surgery and outcome and different techniques such as VNS were available for qualitative analysis, leading to a rather heterogenous group of patients. Fourth, even though we assessed for publication bias, we cannot exclude a general publication bias, due to unpublished negative studies, which are not included. Lastly, we tailored our screening parameters to studies describing a cohort of at least 5 patients under 3 years of age. Therefore, studies addressing pediatric patients older than 3 years were excluded. For VNS, the age was expanded to 5 years to be able to give adequate review. This results in a limited number of patients in the comparative group from only 5 included studies. A selection bias for the comparative cohort must be mentioned.

Conclusion

Epilepsy surgery in pediatric age, especially under the age of 3 years, is a feasible and safe way to treat intractable epilepsy and therefore to potentially prevent severe developmental and cognitive deterioration. Overall seizure outcome is favorable, with slightly more favorable outcomes in the early surgery group. Developmental outcome mostly improves after successful seizure control and reduction of AED is often possible. Overall mortality remained very low while morbidity rates are depended on the underlying pathology and chosen type of surgery; nevertheless, no tendency to more severe complications for younger children could be detected. VNS presents good results and should be more often evaluated as a treatment option not only in palliative situations.

Further comparative studies of prospective nature, analyzing not only seizure but also developmental outcome, should be the focus of future studies.

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Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval No ethics approval is necessary for this review since no primary clinical data has been collected.

Consent for publication Not available since no individual or identifying patient data is published.

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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