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Review

Seizures after cardiac surgery: A systematic review

J. Mengé[1,2], L. Van Laethem[3], E. Hoste[1,3,4], H. Schaubroeck[1,3]

[1]Ghent University, Ghent, Belgium; [2]Department of Anesthesiology and Perioperative Medicine, Ghent University Hospital, Ghent, Belgium; [3]Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium; [4]Research foundation-Flanders (FWO), Brussels, Belgium.

Corresponding author: W. P. Mengé, Ghent University, Ghent University Hospital, Department of Anesthesiology and Perioperative Medicine, Corneel Heymanslaan 10, 9000 Ghent, Belgium. Email: jonathan.menge@ugent.be.

Abstract

Background: **Postoperative seizures are multifactorial and have a possibly underestimated impact on patient outcomes. This systematic review aims to analyze the occurrence rate of postoperative seizures and investigate their effect on outcomes.**

Methods: **The review was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive search of PubMed, Embase, and Web of Science was performed on December 9, 2023. Studies eligible for inclusion were prospective and retrospective studies involving adult patients undergoing cardiac surgery. Review articles, case reports, and studies focused on cardiac interventional procedures, heart transplant surgery, infectious endocarditis, neurosurgery, or vascular/aortic surgery were excluded. Data on seizure occurrence and mortality rates were extracted and analyzed using Excel. Means and interquartile ranges (IQR) were calculated. The risk of bias was assessed using the 2013 Study Quality Assessment Tools from the National Institutes of Health (NIH).**

Results: **Out of 1,644 identified articles, 36 were selected for inclusion. Baseline characteristics revealed heterogeneity in the types of surgery and seizure definitions across the studies. Seizure occurrence rates ranged from 0% to 20% (mean 2.4%, IQR 2.6%) following coronary surgery, 0% to 32.3% (mean 10.4%, IQR 13.1%) following valvular surgery, 0% to 8% (mean 2.3%, IQR 2.1%) in the overall category, and 0% to 9% (mean 2.7%, IQR 2.7%) following open-heart surgery. One study reported a seizure rate of 19.9% for a combined surgery category. In-hospital mortality rates ranged from 1.1% to 29% (mean 12.5%, IQR 13.6%).**

Discussion: **The wide range of seizure occurrence rates observed may be attributable to the heterogeneity between the included studies. Further research is necessary to evaluate the impact of factors such as tranexamic acid (TXA) use, renal function, and other perioperative variables on seizure occurrence. Seizure rates were notably higher following valvular and open-heart surgeries and among patients exposed to TXA. Although limited, available data suggest that patients experiencing seizures may have higher mortality rates, highlighting the need for more robust studies. The review identified a high risk of confounding bias in many of the included studies. Other: This review is registered in The International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42023395374.**

Keywords: **Seizures, Convulsion, Epilepsy, Cardiac surgical procedures, Thoracic surgery, Adults.**

Introduction

Postoperative neurological complications after cardiac surgery are relatively frequent and encompass a variety of clinical entities: thrombo-embolic stroke, short- and long-term memory dysfunction, delirium, cognitive decline, transient neurological dysfunction, and seizures. These all represent a varying degree of neurological injury with important impact on both perioperative and long-term outcome and quality-of-life1–9. Postoperative seizures represent a significant concern with a multifactorial etiology and possibly underestimated impact on outcome measures.

Manuscript will be submitted at University Ghent as dissertation. The abstract will be submitted for presentation at the BeSARPP Graduation Day 2024. The research protocol was submitted at the International Prospective Register of Systematic Reviews (PROSPERO) the 8th of September 2023.

Seizures are caused by sudden, abnormal, excessive, and disorganized discharge of brain cells leading to transient disturbances of cortical function. They can be clinically noticeable or present without noticeable manifestations (subclinical). Clinical manifestations include abnormal motor, sensory and/or psychic phenomena[2,4,5,10–14]. Postoperative seizures may result from thrombo-embolic events, air emboli, release of inflammatory mediators during surgery, metabolic derangements (e.g. hypoglycemia or hyponatremia) and exposure to potentially epileptogenic medication such as antifibrinolytics or cephalosporin antibiotics[15–18].

Previous research has linked different risk factors to postoperative seizures after cardiac surgery. However, these associations have not been consistent among different studies[1,2,4,5,15]. Some of the reported risk factors for seizures include older age, pre-operative neurological disease, pre-operative renal dysfunction, pre-operative cardiac arrest, open-chamber cardiac surgery, prolonged cardio-pulmonary bypass (CPB) time, previous cardiac surgery, deep hypothermic circulatory arrest, aortic calcification or atheroma and critical pre-operative state[1,2,4,10,19]. Different conflicting conclusions are also to be found concerning the impact of postoperative seizures on morbidity and mortality outcomes[1,2].

This systematic review aims at reporting the occurrence rate of postoperative seizures and investigating their impact on outcomes.

Methods

Study Design

A systematic review on seizures after cardiac surgery in adult patients was performed. The study was conducted according to the methodology described in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines anno 202020 This study is registered in the International Prospective Register of Systematic Reviews (PROSPERO), record identification: CRD42023395374.

Search strategy

The scientific search engines PubMed, Embase and Web of Science were used. The search strategy was conducted by one investigator (M.J.) using controlled vocabulary (medical subject headings (MeSH) and Emtree terms), free-text keywords and high-performance search filters. The final search was performed on December 9, 2023, in all databases (Table I).

Study eligibility

Prospective and retrospective studies concerning adult patients, 18 years or older, undergoing myocardial revascularization surgery, valve replacement surgery and valvular repair surgery were held eligible for inclusion. Only full-text articles in English published from 2008 until present were included. Articles before 2008 were excluded, because of the historical shifting point in 2008 where the most common used antifibrinolytic drug changed from aprotinin (Apr) to tranexamic acid (TXA). Review articles, case reports or articles about other types of cardiac surgery, cardiac interventional procedures, heart transplant surgery, infectious endocarditis, neurosurgery and vascular or aortic surgery were excluded.

Article selection

Records were independently screened in Rayyan[21] a research collaboration platform, based on title and abstract by two separate reviewers (V.L.L. and M.J.). Conflicts and unresolved records were resolved using a third independent reviewer (S.H.).

Data extraction

Basic study characteristics (author, year of publication, study design, study period, country, study population) and population characteristics (seizure incidence, type of surgery, outcome measures) were collected and extracted using an

Table I. — Search queries.

Search engine	Search query
PubMed	((seizures[MeSH Terms]) OR (seizures[Title/Abstract]) OR (seizure[Title/Abstract]) OR (convulsion[Title/Abstract]) OR (convulsions[Title/Abstract]) OR (epilepsy[MeSH Terms]) OR (epilepsy[Title/Abstract])) AND ((thoracic surgery[MeSH Terms]) OR (thoracic surgery[Title/Abstract]) OR (cardiac surgical procedures[MeSH Terms]) OR (cardiac surgical procedures[Title/Abstract]) OR (cardiac surgery[Title/Abstract]) OR (heart surgery[Title/Abstract])) AND ((adult[MeSH Terms]) OR (adult[Title/Abstract]) OR (adults[Title/Abstract]))
Embase	('seizure, epilepsy and convulsion'/exp OR seizure:ti,ab,kw OR seizures:ti,ab,kw OR epilepsy:ti,ab,kw OR convulsion:ti,ab,kw OR convulsions:ti,ab,kw) AND ('heart surgery'/exp OR 'heart surgery':ti,ab,kw OR 'cardiac surgery':ti,ab,kw) AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)
Web of Science	(TS=(seizure) OR TS=(seizures) OR TS=(epilepsy) OR TS=(convulsion) OR TS=(convulsions)) AND (TS=(cardiac surgery) OR TS=(heart surgery)) AND (TS=(adult) OR TS=(adults))

Excel (Microsoft) spreadsheet. Occurrence rates of seizures for different types of cardiac surgery (coronary, valvular, combined, overall and open-heart) and mortality rates for different time frames (in-hospital, 30-day, 1-year and >1.5-year) were extracted. Mean and interquartile ranges (IQR) were calculated from collected data for the occurrence rate of seizures per type of surgery and for the mortality rate for different timeframes.

Study risk of bias assessment

A risk of bias assessment was carried out by two raters (V.L.L. and M.J.) using the 2013 Study Quality Assessment Tools from the National Heart, Lung, and Blood Institute (NIH) for observational, case-control and control intervention studies[22].

Results

The systematic literature search identified 1644 records across three databases: 357 from PubMed, 1199 from Embase, and 88 from Web of Science. After screening for duplicates, 209 records were removed, leaving 1435 records for further screening. Two independent reviewers screened the remaining records based on titles and abstracts resulting in the exclusion of 1363 articles. 72 Papers were selected for eligibility. 10 Records were excluded based on the publication date (published before 2008), 6 based on study design, 15 because of unavailability of a full-text article and 5 because of lack of relevant data to extract. Ultimately, 36 studies were included for data analysis (Figure 1).

A prospective study design was used in 15 studies and a retrospective study design in 21 studies. The majority (n=30) of the studies were observational. Five randomized clinical trials (of which 4 double-blinded) and 1 case-control study were included. The different types of cardiac surgery for which data was collected and the definitions of seizures were very heterogeneous. Table II summarizes the different surgery types that were included and definitions of seizures that were yielded in the selected articles.

Risk of bias assessment

A risk of bias assessment, Table III, showed a high risk for confounding bias in a substantial number of included observational studies. This also applied for the case-control study and for the interventional studies. Many papers (22/36) did not provide sample size justification or power description. Furthermore, it is important to consider that seizures were often not the primary endpoint of the articles. This carries an additional risk during the interpretation of the results because the sample size and power analysis has been performed for a different outcome.

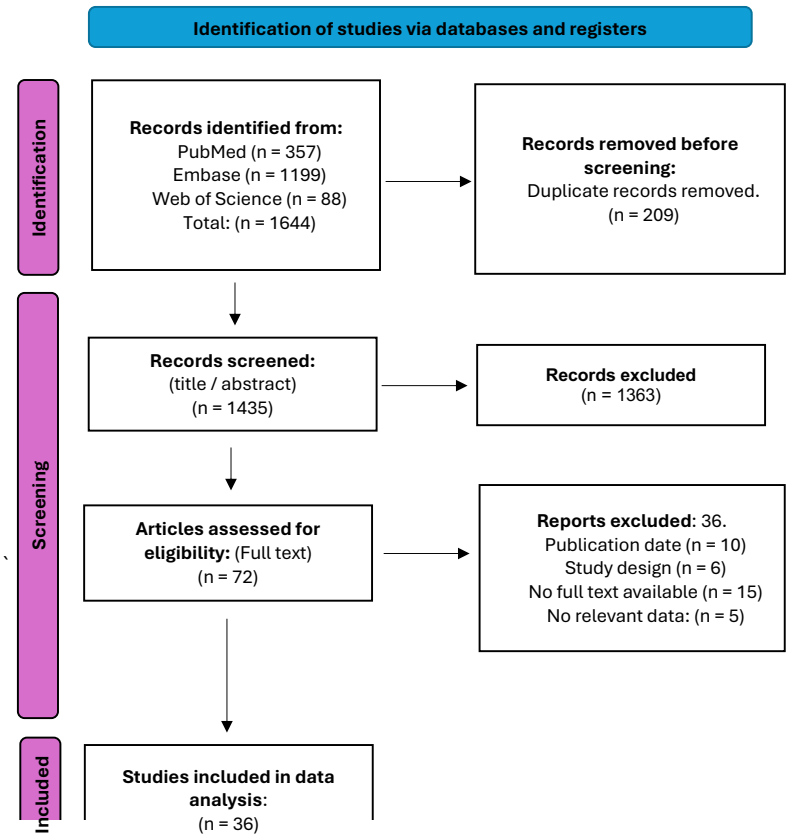

Fig. 1 — PRISMA Flowchart.

Table II. — Baseline characteristics of the included studies.

First author	Year of publi-cation	Study design	Type of data collections	Definitions of seizures	Number of patients included	Type of surgery included	Data about outcome measures
Martin[12]	2008	observational	prospective	clinically diagnosed new seizure	1188	cardiac surgery using CPB	no
Sander[11]	2010	observational	retrospective	clinically apparant convuslive seizure	893	open heart procedures using CPB	no
Keyl[10]	2011	observational	retrospective	generalised seizures	113	AVR +- CABG	yes
Martin[5]	2011	observational	retrospective	clinically diagnosed	604	cardiac surgery using CPB	no
Goldstone[2]	2011	observational	retrospective	sudden episode of transient neurologic symptoms featuring involuntary motor movements, or by EEG in patients with non-convulsive seizures	2578	all types cardiac surgery	yes
Abdollahi[46]	2012	DB-RCT	prospective	convulsions	90	OPCAB	no
Kalavrouziotis[13]	2012	observational	prospective	generalised tonic clonic seizure	8929	cardiac surgery using CPB	yes
Montes[37]	2012	case-control	retrospective	generalised convuslive seizures	140	cardiac surgery using CPB	yes
Manji[4]	2012	observational	retrospective	physician documented	5985	all types cardiac surgery	yes
Koster[41]	2013	observational	retrospective	sudden clonic movement	4883	cardiac surgery using CPB	yes
Gofton[47]	2014	observational	prospective	cEEG	101	all types cardiac surgery	no
Sharma[36]	2014	observational	retrospective	transient episode of disturbed brain function characterized by abnormal involuntary motor movements	11529	all types cardiac surgery	yes
Marcuse[48]	2014	observational	prospecitve	movements suspicious for seizure	723	all types cardiac surgery	yes
Manji[43]	2015	observational	prospective	rhythmic tonic-clonic motion of localized body parts consistent with a focal seizure, or of all four limbs with a decreased level of consciousness consistent with a grand mal seizure	7280	all types cardiac surgery	no
Ivascu[28]	2015	observational	retrospective	convulsive seizure activity or evidence of non-convulsive seizure activity documented by EEG	3518	cardiac surgery using CPB	yes
Brovman[49]	2016	observational	retrospective	not specified	54574	coronary + valvular surgery	no
Couture[23]	2017	observational	retrospective	not specified	12195	cardiac surgery using CPB	no

Table II. — Baseline characteristics of the included studies /2.

First author	Year of publi-cation	Study design	Type of data collections	Definitions of seizures	Number of patients included	Type of surgery included	Data about outcome measures
Zhou[30]	2017	observational	retrospective	new-onset neuropsychiatric disorder with increased motor activity of agitated of hyperactive state	2016	cardiac surgery using CPB	no
Myles[29]	2017	DB-RCT	prospective	convulsions	4662	coronary +- valvular +- CPB	yes
Maeda[50]	2018	observational	retrospective	clinically apparant covulsive seizures	3278	all types of cardiac surgery	no
Jerath[51]	2018	observational	prospective	clincal seizure activity	48	all types of cardiac surgery	no
Abouelella[27]	2019	observational	retrospective	not specified	98	adult congenital cardiac surgery	no
Saracoglu[52]	2019	observational	prospective	not specified	172	open-heart surgery with CPB	no
Habbab[53]	2019	DB-RCT	prospective	not specified	97	cardiac surgery using CPB	no
Verma[26]	2020	RCT	prospective	altered sensorium with up rolling of eyes, with or without tonic-clonic movements of one or more extremities	76	CABG without CPB	no
Tschernatsch[54]	2020	observational	prospective	electroghrapic seizures	100	elective open-chamber cardiac surgery	no
Broadwin[31]	2020	observational	retrospective	not specified	1610	cardiac surgery using CPB	no
Yilmaz[25]	2020	observational	prospective	epilepsy	423	endoscopic CABG	no
Hulde[55]	2021	observational	retrospective	sudden clonic movement	16110	valvular +- coronary	yes
Chandana[24]	2021	observational	retrospective	convulsions	42	CABG + CEA	no
Houthuys[39]	2022	observational	retrospective	witnessed generalized clonic insult or partial insult with or without EEG confirmation	1080	cardiac surgery using CPB	no
Karaarslan[40]	2022	observational	retrospective	convulsive seizure activity	2770	open-heart surgery with CPB	yes
Skhirtladze Dworschak[38]	2022	observational	retrospective	vigilance disorders, abnormal movements such as myoclonus or oral automatisms, presumed seizure activity, confusion, or inadequate wake-up reactions despite no or minimal sedation	1457	cardiac surgery using CPB	yes

Table II. — Baseline characteristics of the included studies /3.

First author	Year of publi-cation	Study design	Type of data collections	Definitions of seizures	Number of patients included	Type of surgery included	Data about outcome measures
Chen[32]	2022	observational	retrospective	new-onset transient dysfunction of the nerve system manifesting as abnormal involuntary. Movementes of the limbs	4124	elective valvular +- coronary	no
Shi[34]	2020	DB-RCT	prospective	generalized tonic-clonic events or focal attacks or mixture of both, persisting for a few minutes	9056	cardiac surgery using CPB	no
Koster[35]	2022	observational	prospective	convulsive seizures	1978	valvular and combined valvular and coronary	no
AVR = aortic valve replacement, CABG = coronary artery bypass graft surgery, cEEG = continuous electro-encephalogram, DB-RCT = double blinded randomized controlled trial, CEA = carotid endarterectomy, OPCAB = off pump coronary artery bypass.							

Table III. — Risk of bias assessment.

Observational studies					
First Author	Quality rating	First Author	Quality rating	First Author	Quality rating
Martin [12] (2008)	fair	Manji[43] (2015)	poor	Yilmaz[25]	poor
Sander[11]	good	Ivascu[28]	poor	Hulde[55]	fair
Keyl[10]	fair	Brovman[49]	poor	Chandana[24]	poor
Martin5 (2011)	fair	Couture[23]	poor	Houthuys[39]	poor
Goldstone[2]	poor	Zhou[30]	fair	Karaarslan[40]	poor
Kalavrouziotis[13]	good	Maeda[50]	good	Skhirtladze Dworschak[38]	poor
Manji[4] (2012)	fair	Jerath[51]	fair	Chen[32]	fair
Koster25 (2013)	good	Abouelella[27]	fair	Koster51 (2023)	fair
Gofton[47]	fair	Saracoglu[52]	fair	Montes[37]	poor
Sharma[36]	poor	Tschernatsch[54]	good		
Marcuse[48]	poor	Broadwin[31]	fair		
Interventional studies		Case-control studies			
First Author	Quality rating	First Author	Quality rating		
Abdollahi[46]	poor	Montes[37]	poor		
Myles[29]	good				
Habbab[53]	fair				
Verma[26]	fair				
Quality rating based on the Quality Assessment Tools from the National Heart, Lung, and Blood Institute (NIH) for observational, case-control and control intervention studies.[22]					

Occurrence rate of seizures for different types of cardiac surgery

Table IV presents the occurrence rate of seizures for different categories of cardiac surgery: overall, coronary, valvular, combined (coronary and valvular) and open-heart surgery.

The occurrence rate of seizures ranged from 0% to 20% with a calculated mean of 2.4% (IQR 2.6%) after coronary surgery, from 0% to 32.3% with a mean of 10.4% (IQR 13.1%) after valvular surgery, from 0% to 8% with a mean of 2.3% (IQR 2.1%) in the overall category and from 0% to 9% with a mean of 2.7% (IQR 2.7%) after open-heart surgery. Only one study reported a seizures rate specifically for the combined category, 19.9% (Table IV).

Some studies investigated specific patient groups. Couture et al. investigated the occurrence rate of seizures in patients undergoing cardiac surgery with a previous history of non-ischemic stroke, Chandana et al. investigated the effect of synchronized versus staged coronary artery bypass graft surgery (CABG) and carotid endarterectomy and Yilmaz et al. investigated the occurrence rate of seizures after endoscopic CABG[23–25]. Abdollahi et al. and Verma et al. specifically investigated patients undergoing off pump coronary surgery. The interventional study of Abdollahi et al. investigated the effect of different medications on postoperative shivering; no convulsions were observed[26]. Verma et al. compared the effectiveness of TXA and epsilon-aminocaproic acid (EACA) on postoperative bleeding in off-pump CABG, they reported one seizure in the TXA group, resulting in a 2.6% occurrence rate[26]. Only one study, Abouelella et al., observed seizures in 6.1% of patients undergoing adult congenital cardiac surgery[27].

Based on logistic regression models, several studies evaluated the effect of surgery type on postoperative seizures: Ivascu et al. found valvular surgery to be an independent risk factor of postoperative seizures (odds ratio (OR) 4.4 (p0.019)), Kalavrouziotis et al. identified open-left sided surgery and Manji et al. identified open-chamber procedures as independent risk factors for seizures (OR 12 (p<0.001) and OR 4.28 (p<0.001), respectively)[4,13,28].

Impact of tranexamic acid

Twelve studies compared the use of tranexamic acid with a different antifibrinolytic drug (aprotinin or EACA), placebo or no tranexamic acid (Table IV). Most of these found significantly higher seizure rates in the TXA groups. However, no studies found higher seizure rates in the TXA group after coronary surgery: Martin et al. compared TXA with aprotinin and reported an occurrence rate of seizures of 0.4% in both groups (p0.98) and Myles et al. compared TXA with placebo and found a frequency of 0.3% and 0.1% of seizures, respectively, (p0.43)[12,29]. Verma et al. reported only one seizure case in the TXA group, this was also not significant in their analysis (p0.98)[26].

All articles concerning valvular and open-heart surgery found significantly higher seizure rates in the TXA groups. Martin et al. compared TXA with Aprotinin after valvular surgery and reported 4.6% and 1.2% (p0.003) of seizures, respectively[12]. Sander et al. compared TXA with aprotinin reporting a seizure rate of 6.7% and 1.9% (p0.05), respectively, and Myles et al. compared TXA with placebo and found 2% and 0% of seizures (p0.003), respectively, both after open-heart surgery[11,29].

For the overall category, all papers, accept Zhou et al., Broadwin et al. and Chen et al., reported significantly higher seizures rates in the TXA group (all p values <0.05)[30–32].

The study of Hulde et al. found that the use of TXA and pre-operative stroke both were independently associated with higher rates of seizures in patients undergoing valvular open-heart surgery. However, no significant interaction between TXA and pre-operative stroke could be established[33]. Two papers, Shi et al. and Koster et al., compared different dosage protocols for TXA, only one, Shi et al., showed significantly higher seizure rates for higher dosages of TXA[34,35].

Three studies were able to identify TXA as an independent risk factor for postoperative seizures based on a multivariable analysis: Sharma et al. (OR 14.3 (p<0.001)), Kalavrouziotis et al. (high-dose TXA: overall category OR 2.6 (p<0.0001) and isolated CABG OR 3.3 (p0.03)) and Manji et al. (OR 7.35 (p<0.0001))[4,13,36].

Impact of renal function

Several studies analyzed the effect of renal function on the occurrence rate of seizures. However, only a few were able to identify renal function parameters as independent risk factors for postoperative seizures based on logistic regression models.

Ivascu et at. found renal insufficiency (as define in the New York State Departement of Health Database) to be associated with early seizures, OR 1.0 (p0.003)[28]. Kalavrouziotis et al. reported pre-operative renal failure as an independent risk factor for early seizures (within 24 hours postoperative), OR 3.3 (p<0.001). This paper also reported significantly more postoperative renal failure in the seizure group compared to patients without seizures (p<0.001)[13]. The case-control study of Montes et al. identified preoperative serum

creatinine >1.29 mg/dL and estimated glomerular filtration rate (eGFR) assessed by the Modification of Diet in Renal Disease equation (MDRD) <59 mL/min per 1.73m2 as predictors for postoperative seizures, with an OR of 3.4 (p=0.01) and 1.87 (p=0.01), respectively[37].

Table IV. — Occurrence rate of seizures (%) for types of surgery.

Occurrence rate (%) per type of surgery					
	Coronary	Valvular	Combined	Overall	Open-heart
Martin[12] (2008)	TXA: 0.4 Apr: 0.4	TXA: 7.9 Apr: 1.2		TXA: 4.6 Apr: 1.2	
Sander[11]				TXA: 2.7 Apr: 0.9	TXA: 6.7 Apr 1.9
Keyl[10]				TXA 6.4 EACA: 0.6	
Martin[5] (2011)				TXA: 7.6 EACA 3.3	
Goldstone[2]	3.2	32.3	19.9	1.2	
Abdollahi[46]	0				
Kalavrouziotis[13]				1.3	
Montes[37]				3.5	
Manji[4] (2012)				0.9	2.4
Koster25 (2013)				TXA: 2.5 No TXA: 1.2	
Gofton[47]				3	
Sharma[36]				0.9	1.5
Marcuse[48]				0.8	
Manji[43] 2015	0.2			0.8	0.6
Ivascu[28]				1.3	
Brovman[49]	0.0	0.1			
Couture[23]	NIS: 0.2			NIS: 1.2	
Zhou[30]				TXA: 1.2 No TXA: 1.2	
Myles[29]	TXA: 0.3 Placebo: 0.1			TXA: 0.7 Placebo: 0.1	TXA: 2 Placebo: 0
Maeda[50]				TXA: 6.9 No TXA: 2.7	
Jerath[51]				TXA: Low risk: 0 High risk: 8	
Abouelella[27]				6.1	
Saracoglu[52]					0
Habbab[53]				1	
Verma[26]	TXA: 2.6 EACA: 0				
Tschernatsch[54]					9
Yilmaz[25]	1.2 (endo CABG)				
Broadwin[31]				EACA: 0 TXA: 0.1	
Hulde[55]					No stroke + No TXA: 1.1 Stroke + No TXA: 3.2 No Stroke + TXA: 2.9 Stroke + TXA: 6.9
Chandana[24]	CABG + CEA: Staged: 4.5 Synchronous: 20				

Table IV. — Occurrence rate of seizures (%) for types of surgery /2.

Occurrence rate (%) per type of surgery					
	Coronary	Valvular	Combined	Overall	Open-heart
Houthuys[39]				0.6	
Karaarslan[40]					0.9
Skhirtladze-Dworschak[38]				6.1	
Chen[32]				TXA: 2.7 No TXA: 2.4	
Shi[34]				TXA: High dose: 1.0 Low dose: 0.4	TXA: High dose: 1.2 Low dose: 0.4
Koster[35]					TXA: Moderate dose: 3.8 Low dose: 4.1
Range	0-20	0-32.3	19.9	0-8	0-9
Mean (IQR) (%)	2.4 (2.6)	10.4 (13.1)	/	2.3 (2.1)	2.7 (2.7)

Occurrence rate for seizures in percentages for different types of cardiac surgery. Different study groups displayed when available. Calculated mean and IQR displayed below. IQR = interquartile range; TXA= tranexamic acid; Apr= aprotinin; EACA= epsilon aminocaproic acid; NIS= non-ischemic seizure; Low / High risk= referring to low- and high-risk surgery groups; endo CABG= referring to endoscopic CABG; CEA= carotid endarterectomy.

Mortality rate of patients who had seizures after cardiac surgery

A total of 11 papers displayed mortality rates for patients with seizures after cardiac surgery. Only one paper reported mortality rates for a selective type of surgery group (Table V).

Most of the studies reported in-hospital mortality rates. Five studies included 30-day mortality, 2 included 1-year mortality and >1.5-year mortality rate was studied in one article (Table V). Additionally, Myles et al., published a relative risk for of 30-day mortality in patients with seizures from a post-hoc analysis[29].

In-hospital mortality

The in-hospital mortality rate of patients after cardiac surgery with seizures ranged from 1.1% to 29% with a calculated mean of 12.5% (IQR 13.6). (Table V) Goldstone et al., Skhirtladze-Dworschak et al. and Sharma et al. demonstrated significantly higher in-hospital mortality rates in

Table V. — Mortality among patients who experienced seizures after cardiac surgery.

Mortality rate (%)				
	In-hospital	30-day	1-year	>1.5-year
Goldstone[2]	29		47	
Kalavrouziotis[13]	6.7			
Montes[37]	14.3			
Manji[4] (2012)	21.3			
Koster[41]	Overall: TXA 19.1 No TXA 6.4 Coronary: TXA 1.5 No TXA 1.1			
Sharma[36]	7			
Marcuse[48]	20			
Ivascu[28]		6.7		
Hulde[55]	3.6	4.0		
Karaarslan[40]		16	0	28
Skhirtladze-Dworschak[38]	24	3		
Range Mean (IQR)	1.1-29 12.5 (13.6)	3-16 8.9 (6)	0-47 23.5 (23.5)	/

Mortality rate for different time frames displayed in percentages. Different study groups displayed when available. IQR = interquartile range.

patients with seizures compared to patients without seizures (p-values <0.001, <0.001 and 0.012, respectively)[2,36,38].

Mortality at 30 days

Four papers reported on mortality at thirty days after surgery, the mortality rate ranged from 3% to 26% with a calculated mean of 8.6% (IQR 6%) (Table V). Two out of four studies, Houthuys et al. and Karaarslan et al., showed significantly higher 30-day mortality in patients with seizures (p=0.02 and <0.01, respectively)[39,40]. Contrary, Ivascu et al. was not able to identify seizures as an independent risk factor for 30-day mortality based on a logistic regression model[28].

Long-term mortality

Two papers reported a one-year mortality rate, Goldstone et al and Karaarslan et al. (Table V). Goldstone et al. found a one-year mortality rate of 47%, significantly higher compared to patients without seizures (p<0.001)[2]. Karaarslan et al. did not report any deaths at one-year post cardiac surgery and reported a one-year morality rate of 0%. This study also reported a >1.5-year mortality rate, 28%, and found it to be significantly higher compared to patients without seizures (p<0.01)[40].

Exposure to Tranexamic acid and mortality

Koster et al. analyzed mortality rates for patients with seizures with or without the use of TXA (Table V). In-hospital mortality rates were found to be significantly higher for patients with seizures in both the TXA and reference group (p<0.003 and 0.03, respectively). The usage of TXA was also found to be associated with higher in-hospital mortality. Their investigations suggest that the observed increased mortality after receiving TXA is independent of the absence or presence of seizures[25].

Discussion

A total of 36 studies were analyzed in this systematic review on the occurrence and mortality rate of seizures after cardiac surgery.

Occurrence rate of seizures for different types of cardiac surgery

We found that seizures occurred in on average 2.3% (IQR 2.1%) of patients after cardiac surgery, considering the overall surgery category, with an important variation between the different studies. The large range between the observed occurrence rates in the different studies might be due to the heterogeneity of the analyses included in the review.

First, large differences exist in included population between the several trials. The literature search and article selection were designed to exclude cardiac interventional procedures, heart transplant surgery, infectious endocarditis surgery, neurosurgery and vascular or aortic surgery. However, some of the included papers may still contain data from these types of surgery, since this is not often described in detail in the included studies. Aortic surgery, often associated with deep hypothermic cardiac arrest, surgery for infectious endocarditis and heart transplant surgery are known to be associated with a higher incidence of neurological complications (due to specific mechanisms: thrombo-embolic, stroke, septic emboli, and medication side effects…). Additionally, some studies excluded patients with seizures suffering from concomitant stroke while others did not.

Secondly, as already mentioned, the definition of seizures varied between the different studies. These ranged from evident tonic-clonic motor movements to more subtle involuntary motor movements. Likewise, the registration of seizures often depended on a clinical observation by medical or nursing staff. Most of the studies did not implement a systematic screening for clinical seizures. Non-clinical seizures could have gone uncaptured since EEG was seldom routinely performed. This might account for a lower occurrence rate in retrospective observational studies based on post-hoc medical record screening.

Furthermore, most of the included studies are observational, which increases the risk of bias. None of the interventional studies were specifically focused on seizures and used the occurrence of seizures as a secondary endpoint or as a part of a combined endpoint.

Few articles reported detailed results concerning the occurrence rate of seizures for different cardiac surgery types. However, some of them were able to identify valvular and open-heart surgery as an independent risk factor. This might be due to a possibly higher rate of thrombo-embolic events, air-emboli and longer CPB time.

Impact of tranexamic acid

TXA has also been associated with higher rates of seizures and could be identified as an independent risk factor in several studies. TXA is the most used antifibrinolytic drug during cardiac surgery since 2008. TXA crosses the blood-brain barrier (BBB), especially in circumstances where the BBB has been compromised and binds competitively, in a dose-dependent fashion, to y-aminobutyric acid (GABA) type A receptors. This results in reduced inhibitory activity and increased neuronal

excitation and might explain the observed higher seizure rates[42].

Impact of renal function

A comprehensive analysis of preoperative and postoperative renal function measures was not included in this systematic review. While Manji et al. found a significant association between elevated preoperative creatinine levels and recurrent seizures, a more detailed investigation is necessary to draw well-supported conclusions on this topic[43]. A deeper exploration of the literature would help provide a more robust understanding of the relationship between renal function and seizure outcomes.

Additional possible perioperative factors

Several potential risk factors that brought forward throughout the different studies, were not extensively analyzed in this systematic review. These include older age, preoperative neurological and cognitive state, duration of CPB, temperature management, impact of redo surgery, peripheral vascular disease, aortic calcifications or atheroma and critical pre-operative state[1,2,4,10,19,43].

Perioperative neuromonitoring and neuroprotection are topics that rarely occurred in the reviewed literature. Studies often describe general perioperative management and standard protocol mentioning temperature management, de-airing techniques, and specifics concerning cannulation. However, more detailed intraoperative data has not been reported which might differ between studies and might influence occurrence of postoperative seizures.

Data on the use of other epileptogenic drugs was limited throughout the analyzed articles. Cephalosporin antibiotics were often mentioned in the description of the perioperative anesthetic management but did not receive further attention.

Mortality rate

The number of studies that reported mortality outcome measures was limited. Several articles could demonstrate significantly higher mortality rates four different timeframes in patients suffering from postoperative seizures compared to patients without seizures. We found the in-hospital mortality to be 12.5% (IQR 13.6), on average. Data also shows that the usage of TXA was associated with a higher in-hospital mortality rate compared to no usage of TXA, most likely independently from the presence or absence of seizure.

The mechanism behind higher mortality rates in patients with seizures has not been evident throughout literature. It is possible that the effect is substantially based on confounding mechanism. Further analysis and additional research is necessary to further evaluate the impact of postoperative seizures on mortality outcomes.

Clinical implementation and future research directions

Given that seizures are a significant, potentially treatable complication with a substantial impact on patient outcomes, early detection, prevention, and treatment are essential, as they can mitigate brain injury and reduce other indirect negative impacts (e.g. prolonged mechanical ventilation, extended sedation, and longer ICU and hospital stays).

Well trained and experienced medical staff is essential in the early detection and diagnosis of seizures. Sensibilization, medical staff training and development of clinical protocols directed to high-risk patient groups is desired in clinical practice.

As seizures often go subclinical or occur in sedated patients, neuro-monitoring is crucial in managing seizures. EEG monitoring is most often used to detect and confirm seizures. Several other neurological monitoring modalities (e.g. near-infrared spectroscopy (NIRS) neuroimaging, serum injury biomarkers and intracranial pressure (ICP) monitoring, somatosensory-evoked potentials (SEP), serial head ultrasounds (HUS)) are less frequently used, but could become more relevant in the future of seizure management[44,45].

Future research is needed to determine whether other neurological monitoring modalities could be beneficial in the routine management of postoperative seizures. Additionally, more studies are also required to further identify risk factors and implement possible preventative measures.

Strengths and limitations

The systematic literature search and article selection was extensive and was carried out according to standard guidelines. The screening process was performed thoroughly, and the article characteristics display the heterogeneity within the different studies, especially concerning the definition of seizures and the included surgery types. Data for the occurrence rate of seizures occurring for different types of cardiac surgery was largely observational and data concerning long-term outcome was limited. No meta-analysis was performed.

Firm conclusions could not be drawn due to this heterogeneity and low-quality data.

Furthermore, data concerning TXA should be interpreted with caution. This review did not aim to address the question whether TXA is linked to seizures.

Conclusion

Seizures occurred in 2.3% of patients undergoing cardiac surgery. There was a considerable heterogeneity between studies. Seizure rates were higher after valvular and open-heart surgery. Exposure to TXA was in several studies associated with higher occurrence rates of seizures. Mortality rates was higher for patients suffering from postoperative seizures; however, data was limited.

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