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Contrast-induced encephalopathy following intra-arterial iodinated contrast media injection in patients with atherosclerotic cardiovascular disease: A retrospective analysis

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Abstract

Background & Objective: This study examined the current status of contrast-induced encephalopathy (CIE) following intra-arterial iodinated contrast media injection in patients with atherosclerotic cardiovascular disease (ASCVD). Specifically, we aimed to examine the clinical, epidemiological characteristics, pathogenic mechanisms, and clinical symptoms of CIE in patients with ASCVD in order to promote its prompt diagnosis and treatment. *Methods:* Chinese and English scientific databases were searched using the following search terms: atherosclerotic cardiovascular disease, contrast-induced encephalopathy, neurotoxicity, encephalopathy, brain injury, cortical blindness, cerebral/carotid arteriography, cardiac catheterization, coronary angiography, percutaneous coronary intervention, and peripheral arteriography. The retrieved articles and references of the primary articles were used to collect the basic information. SPSS 20.0 and Excel statistic software were used to conduct this retrospective analysis. *Results:* A total of 89 cases consisting of 87 patients were identified. Of all the patients, 59 (67.05%) were male. Patients had an average age of 67.12 + 10.51 years. In addition, 64 (73.56%) had hypertension, 26 (29.89) had diabetes mellitus, 14 (16.09%) had renal impairment, and 5 (5.75%) had old cerebral infarction or transient cerebral ischemia. The mean and median volumes of administered iodinated contrast media were 228.41 and 190 ml, respectively (range: 25–1500 ml). The symptoms included cortical blindness (24.72%), delirium (13.48%), hemiplegia (10.11%), seizure (8.99%), and ophthalmoplegia (5.62%). The symptoms typically appeared within minutes to hours following the contrast administration and always resolved entirely within 24–72 hours. Only 4 patients suffered irreversible damage; 1 of these patients died after 56 days of treatment.
Conclusions: CIE is a rare complication during the intervention procedure. It has variable presentations with an excellent prognosis. Nevertheless, it can result in clinical complications, such as neurological sequelae or even death on rare occasions. Therefore, physicians should pay close attention to implementing appropriate measures.

Keywords: Atherosclerotic cardiovascular disease, contrast-induced encephalopathy, brain injury, retrospective analysis, case report.

INTRODUCTION

The incidence of cardiac catheterization-associated cerebrovascular complications is estimated to range between 0.05-0.10% for diagnostic coronary angiography and 0.12-0.40% for percutaneous coronary intervention (PCI). Additionally, the neurological adverse effects of contrast media used for cerebral angiography have an estimated 1–2% prevalence rate.[2] Contrast-induced encephalopathy (CIE) is an acute but reversible neurological disturbance associated with the intra-arterial administration of an iodinated contrast medium during an intervention procedure. Its symptoms may manifest as encephalopathy, motor and sensory and vision disturbances, including cortical blindness, ophthalmoplegia, aphasia,

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and seizures. The syndrome's pathophysiology is mainly implicated due to the disruption of the blood-brain barrier and direct neuronal toxicity. Generally, CIE following intervention procedures is rare and sparsely documented in the literature. All previous studies[2-13] have mainly focused on the sporadic case reports. Therefore, the current study focuses on the patients with CIE following atherosclerotic cardiovascular disease (ASCVD). A descriptive analysis was conducted for the epidemiological characteristics, risk factors, clinical symptoms, and prognosis in this retrospective research. The study's outcome will help the clinicians broaden their understanding of the disease's diagnosis treatment and lay the foundation for further studies.

METHODS

Study population

We searched scientific databases including PubMed, OVID MEDLINE, CNKI, Embase, and Wan Fang, using various combinations of the following search terms: atherosclerotic cardiovascular disease, iodine contrast, neurotoxicity, encephalopathy, contrast-induced encephalopathy, cortical blindness, coronary angiography, cardiac catheterization, and percutaneous coronary intervention in the English and Chinese languages from 1970 to June 2020. In addition, the reference lists of each article were retrieved, manually searched, and cross-checked.

Definitions

The National Lipid Association (2014) defined ASCVD as the myocardial infarction, acute coronary syndrome, coronary revascularization, ischemic stroke or transient ischemic attack, a peripheral arterial disease with an ankle-brachial index < 0.9, renal atherosclerosis, aortic aneurysm from atherosclerosis, and carotid plaque ≥ 50% stenosis.[1]

The diagnosis of CIE is based on the symptoms and signs of neurological dysfunction such as 1) temporally related to intervention procedures, manifesting within minutes to hours of the administration of the iodine-based contrast agent; and 2) not attributable to other pathological processes, including cerebrovascular ischemia or hemorrhage, seizure disorder, metabolic abnormalities and drugs, arterial dissection, and air embolization. Delirium was defined as an acute-onset mental state that included confusion, dysphoria, paraphasia, inattention, and difficulty orienting to a place or person. A seizure was defined as sudden confusion with limb convulsion. Onset time was defined as the time from the end of surgery until the appearance of the first CIE symptom.

Statistics

Continuous variables were presented as mean±standard deviation and compared using unpaired Student's t-tests. Categorical data were presented as frequencies and compared using x^2 or Fisher's exact tests. Finally, the correlations were examined using Pearson's tests. A $p < 0.05$ was considered statistically significant.

RESULTS

Baseline demographics

We identified a total of 89 cases (8 case series and 54 case reports) for 87 patients. Of these patients, 2 (1 male and 1 female) experienced recurrent CIE in several years. The patient's clinical data are detailed in Supplementary Table S1.[2-63] Of the 88 patients, 59 (67.05%) were male, and 28 (32.95%) were female. Patient's ages conformed to a normal distribution, with a minimum of 39, a maximum of 89, with an average of 67.12 ± 10.51 years. see Table 1).

Hypertension, diabetes mellitus (DM), and renal impairment were suggested as risk factors of CIE. We collected the patient's medical history for hypertension, DM, chronic kidney disease (CKD), including renal impairment and renal dialysis. We also examined the patient's medical history to identify patients with an old cerebral infarction (OCI) or transient cerebral ischemia (TIA). There were 64 (73.56%) hypertensive and 23 (26.43%) non-hypertensive patients. The proportion of hypertension was 1.78 times higher than non-hypertension. There were 26 DM (29.89%) patients and 61 (70.11%) non-DM patients. 14 (16.09%) patients had CKD, 5 patients (5.75%) had a history of OCI or TIA, 18 patients had both hypertension and DM. Total 9 patients had both hypertension and renal impairment, 2 had DM and CKD, and 2 had the merging of 3 factors (see Table 1).

Of the 89 cases of 87 patients, 72 (80.90%) had coronary heart disease. Specifically, 13 (14.61%) patients had an acute myocardial infarction, and 59 (66.29%) had unstable or stable angina pectoris (of these, 2 were diagnosed with unstable pectoris

Table 1: The baseline data of all CIE cases

Variables		Number (n)	Percent (%)
Age (yrs)			
	~40	1	1.12
	41~50	5	5.62
	51~60	14	15.73
	61~70	27	30.34
	71~80	32	35.96
	81~90	9	10.11
	Unknown	1	1.12
Gender			
	Male	59	67.05
	Female	28	32.95
Previous history			
Hypertension	Yes	64	73.56
	No	23	26.43
Diabetes mellitus	Yes	26	29.89
	No	61	70.11
CKD	Yes	14	16.09
	No	73	83.91
OCI/TIA	Yes	5	5.75
	No	82	94.25
Diagnosis of disease distribution			
CHD		72	80.90
	AMI	13	14.61
	AP	59	66.29
Carotid/cerebral artery stenosis		12	13.48
Renal artery stenosis		3	3.37
Other peripheral vascular diseases		2	2.25
Procedure patients underwent			
	Angiography	35	46.07
	Diagnostic and Stenting	53	59.55
	Transcatheter aortic valve replacement	1	1.12
Total		89	100.00

Abbreviations: CKD, chronic kidney disease including renal impairment or patients who needed renal dialysis; OCI, old cerebral infarction; TIA, transient cerebral ischemia; AMI, acute myocardial infarction; AP, angina petites; ACI, acute cerebral infarction.

twice, respectively). In addition, 12 (13.48%) patients had a cerebral vascular disease and acute cerebral infarction (ACI) and TIA, and 3 (3.37%) had renal artery stenosis. Additionally, 2 patients (2.25%) were diagnosed with other peripheral vascular diseases, and 1 patient was diagnosed with 100% obstruction of the right common iliac artery (see Table 1).

Procedure patients underwent

A total of 35 (46.07%) patients underwent diagnostic procedures, including coronary artery angiography, carotid artery angiography, cerebral

artery angiography, renal artery angiography. While 53 (59.55%) patients underwent diagnostic and stenting, including PCI and carotid artery stenting, and 1 (1.12%) patient underwent transcatheter aortic valve replacement (see Table 1).

Type and volume of iodinated contrast media

Iodinated contrast media can be categorized based on their physical and chemical characteristics, such as chemical structure, osmolarity, iodine content, and the ionization properties in the solution.[2] Contrast media compounds may be monomeric or dimeric. Monomeric contrast molecules contain 1 benzene ring and 3 iodine atoms. In addition, iodinated contrast compounds may be ionic or non-ionic. Ionic compounds break up into anion and cation components in a solution, whereas non-ionic compounds do not. In this study, the mean and median volumes of administered iodinated contrast media were 228.41 and 190 ml, respectively (range: 25–1500 ml). High-osmolarity contrast media was used in 8.99% (8/89) of cases, while low-osmolarity contrast media and iso-osmolar compounds were used in 73/89 (82.02%) and 1/89 (1.12%) of patients, respectively (see Table 2).

Clinical manifestations, treatments, and outcomes of CIE patients

Concerning symptomatology, emotion and sensory disturbances, encephalopathy, vision disturbance, ophthalmoplegia, hemiplegia, global aphasia, and seizures were described. Transient cortical blindness was the most common manifestation of CIE and occurred in 23 of the 89 (24.72%) cases. The other reported symptoms included delirium (13.48%), hemiplegia (10.11%), seizures (8.99%), and ophthalmoplegia (5.62%). Non-specific symptoms such as dizziness, headache, and restlessness occurred in 30.08% of cases (see Table 3).

Most of the patients (71/89; 79.78%) received only supportive treatment, 5 patients underwent dialysis or hemodialysis, 5 patients received intubation and ventilation, 2 patients received cardiopulmonary resuscitation (CPR), and 1 patient had a temporary transvenous pacemaker installed. Most of the patients (85/89; 95.51%) recovered completely, and only 4 patients suffered from irreversible damage (1 suffered from right-hand muscle strength decline, 1 suffered from blepharoptosis and diplopia, 1 suffered from persistent forgetfulness with vision loss, and 1 patient died from CIE after 56 days of treatment).

Table 2: The type and volume of iodinated contrast media used

Contrast media	Type	Number (n)	minimal volume (ml)	maximum volume (ml)	median volumes (ml)	Mean volumes (ml)
CM	iodinated	89*	25.00	1500.00	190	228.41
diatrozoate	high-osmolarity, ionic monomer	8	48.00	800.00	219	294.00
iobitridol	low-osmolarity, ionic dimer	1	75.00	75.00	75	75.00
iodixanol	low-osmolarity, non-ionic monomer	13	50.00	350.00	150	176.92
iohexol	low-osmolarity, non-ionic monomer	9	100.00	250.00	180	165.56
iomeprol	low-osmolarity, non-ionic monomer	7	150.00	500.00	320	337.14
iopamidol	low-osmolarity, non-ionic monomer	8	80.00	415.00	250	233.89
iopromide	low-osmolarity, non-ionic monomer	22	25.00	300.00	155	174.09
ioversol	low-osmolarity, non-ionic monomer	6	100.00	370.00	226	225.33
ioxaglate	iso-osmolar, non-ionic dimer	1	230	230.00	230	230.00
unknown	unknown	7	-	-	-	-

Note:*the contrast media volume of 11 cases is unknown, including 3 cases of iohexol;1 case of iopamidol, and 7 cases without the name and type of the contrast media information.

Table 3: Clinical manifestations and symptom duration of CIE patients

Variables	Number (n)	Percent (%)
Clinical manifestations		
Cortical blindness	22	24.72
Ophthalmoplegia	5	5.62
Seizures	8	8.99
Hemiplegia	9	10.11
Delirium	12	13.48
Nonspecific symptoms	33	30.08
Symptom duration (hrs)		
<6h	12	13.48
6~12h	10	11.24
12~24h	17	19.10
24~48h	20	22.47
48~72h	11	12.36
72~96h	2	2.25
96~120h	8	8.99
>120h	9	10.11
Total	89	100.00

Abbreviations: h, hours.

Onset time and duration

Symptoms and signs of neurological dysfunction manifested within minutes to hours (up to 72 hrs) post-surgery and the administration of an iodine-based contrast agent. Most patients, 78.82% (67/85), recovered fully within 72 hrs; however, 22.35% (19/85) needed more time to recover. The median time to complete symptom resolution was 31 hrs. The relief time was unrelated to age, dosage, or risk factors (see Table 3).

Neuroimaging by CT/MRI

CIE diagnosis requires the absence of hemorrhage or embolism demonstrated by neuroimaging using computed tomography (CT) or magnetic resonance imaging (MRI). The most commonly reported abnormalities on the CT brain scans were cortical or subcortical contrast enhancements. Other findings included cerebral edema, focal hyperdense lesions, and hyper densities in the cerebral sulci. However, in the 24 cases, neuroimaging was normal.

DISCUSSION

With the ever-growing use of vascular intervention for diagnostic and therapeutic methods (including cerebral/carotid arteriography, cardiac catheterization, and peripheral arteriography), associated complications are more likely to arise. CIE is a rare complication resulting from the contrast-based procedures of arterial access. The neurological adverse effects of contrast media from invasive cerebral angiography have a prevalence rate of 1–2%.[64] However, CIE following cardiac catheterization procedures is rare, with a prevalence rate of 0.05–0.4%.[65,66] The contrast media investigations, including carotid arteries and vertebral circulation interventions, are frequently but rarely associated with CIE. The CIE cases after coronary artery angiography have been first reported as far back as 1970.[62] So far only Spina *et al*. has summarized five case series and 38 case reports, for a total of 52 patients who recovered well[67]; while we collected a larger number of 89 patients, including 4 cases suffered from irreversible damage even death.

The precise mechanism of CIE is poorly understood. However, the physical and chemical properties of contrast media can result in the osmotic disruption of the blood-brain barrier. In contrast, the hyperosmolarity and direct neurotoxicity of extravasated contrast media cause cerebral edema.[68] Theoretically, the incidence of blood-brain barrier disruption should be higher

with hyperosmolar contrast media use than the lower osmolarity or iso-osmolar contrast media used. This phenomenon is associated with the former contrast media greater osmotic force on the endothelial cells in cerebral arterioles, capillaries, and venules, causing cell shrinkage and cell separation at tight junctions and promoting flow into the extravascular compartment.[68-70] However, previously we have reported that CIE occurs with both high- and low-osmolar solutions and even with iso-osmolar solutions.[29] The hyperosmolarity of contrast media and its blood-brain barrier permeability can cause contrast extravasation to the cerebral space, while the iso-osmolar contrast medium can induce CIE.[32] The occipital cortex is the most vulnerable region, as it is the primary region of the blood-brain barrier with high permeability.[71]

Additionally, the uncontrolled elevation of systemic blood pressure can exceed the autoregulatory capacity of the cerebral vessels, compounded by an elevation in intraluminal pressure arising from the pressure injection of the contrast media. This cascade leads to increasing vascular wall tension and widens gap junctions, resulting in the blood-brain barrier breakdown. With the disruption of the blood-brain barrier, the extravasation of contrast media to the interstitial space causes the direct stimulation of neural cells and results in neurotoxicity. However, the mechanism of direct neuronal toxicity is not yet clear. Therefore, further research is required to delineate the mechanism of CIE.

Patients with chronic hypertension, male gender, impaired cerebral autoregulation, transient ischemic attack, impaired renal function, large contrast volumes, and the selective angiography of internal mammary grafts are at a higher risk of developing the condition.[71-73] In our study, most patients with transient encephalopathy following intra-arterial contrast injection had a history of chronic hypertension (63/88) and were male (71.59%). The presence of precedent TIA and OCI, coupled with the altered permeability of the blood-brain barrier, could have predisposed patients to CIE. Besides, impaired renal function leads to decreased clearance and prolonged exposure to contrast media. However, the relationship between contrast medium volume and CIE remains unclear. Although large contrast volumes are more likely to cause CIE, a study has shown that a local injection of 25 mL of contrast medium to the carotid artery could also cause CIE.[30]

The presentation of CIE is highly variable and ranges from subtle (such as headache) to more extreme features (such as coma or unresponsiveness). It may also manifest with localized cortical and subcortical deficits (e.g., hemiparesis, hemianopia, cortical blindness, and speech changes) and global syndromes (e.g., confusion, seizure, and coma).[74-76] In our study, 24.72% of patients had cortical blindness, 13.48% had delirium, 10.11% had hemiplegia, 8.99% had seizures, and 5.62% had ophthalmoplegia. Furthermore, 30.08% of patients had non-specific symptoms, including dizziness, headache, and restlessness. However, cortical blindness was the most common symptom. On rare occasions, CIE may result in fatal cerebral edema.[80] Unfortunately, a female patient died in this study following 56 days of CIE.[8] Currently, no effective treatment is available for such severe fatal CIE. However, in one study, Junck and Marshall[78] reported that iodine concentrations in patient's post-mortem tissues such as urine, serum, and kidney were the highest. Thus, continuous renal replacement therapy and blood purification may be potential treatments for cases of fatal CIE.

The symptoms of CIE typically appear soon after the end of the surgery or after contrast administration as reported. The neurological deficits last from 15 minutes to 5 days in most cases. In this retrospective research study, onset time was defined as the time from artery injection to onset of clinical symptoms to avoid the effects of surgery duration on the results. The shortest onset time was less than 5 minutes after contrast administration. The finding suggests that cerebral vasospasm and contrast-induced hypersensitivity may play essential roles in the pathogenesis of CIE.[79] Given these uncertainties and the rare occurrence of CIE, the definite recommendations beyond general safety measures are difficult to apply in all patients undergoing a procedure with contrast. However, we recommend that the contrast volume be kept to a minimum with the well-hydrated state of patients before and after the procedure. We also recommend using isotonic, non-ionic contrasts, especially in patients at high risk of encephalopathy.

In most cases of CIE, the prognosis has been excellent, with rapid recovery (with only supportive therapy). It is recommended in the immediate postprocedural period that intravenous hydration should be used, and patients are closely monitored. An anti-convulsant to treat seizures and intravenous mannitol and methyl-prednisone have been used to reduce cerebral edema without adverse consequences.[32] On rare occasions, CPR, intubation, and ventilation were also used. In our

analysis, 2 patients suffered from recurrent CIE, while 4 suffered from irreversible damage, out of which 1 patient died from CIE after 56 days of treatment. This case represented a significantly prolonged neurological recovery time with a very unfortunate ending compared to similar cases with normal CT findings.

Close monitoring is vital as some of these patients may deteriorate and require a high-dependency level of care. Recognition of CIE at an early stage is crucial to exclude potentially detrimental neurologic presentations, such as ischemic or hemorrhagic events. Early diagnosis can also prevent the inappropriate administration of potentially harmful treatment, such as thrombolysis. Follow-up examinations after discharge are essential to identify any residual neurological deficits.

In conclusion, CIE is a rare complication but has a good prognosis during an intervention procedure. However, it can give rise to some clinical complications, such as neurological sequelae or even death in rare cases. Therefore, doctors performing angiography and interventions should be aware of its severe and potentially harmful effects. Due to its rare occurrence, preventing severe contrast-induced complications are very difficult. Further studies are warranted to define the risk factors and the mechanism associated with iodinated contrast agent neurotoxicity to help minimize the severe complications.

DISCLOSURE

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Supplementary Table 1: The baseline data of all cases included

Study/year	gender	age	HT	DM	TIA/OCI	CKD	Contrast	Contrast Volume (ml)	diagnose	procedure
Harada, 2020[2]	F	72	yes				-	210	STEMI	CAG+PCI
Lei, 2020[3]*	M	76	yes	yes	yes		iodixanol	80	UAP	CAG
	M	76	yes	yes	yes		iodixanol	150	UAP	CAG+PCI
Neilan, 2019[4]	M	81	yes				iopamidol	250	CAD, abdominal aortic aneurysm, peripheral vascular disease	TAVR transcatheter aortic valve replacement
Renault, 2019[5]	M	49	yes			yes	iohexol	-	Renal artery stenosis	renal artery angiography
Defalco, 2019[6]	F	82	yes			yes	iohexol	-	atheromasic coronaries	CAG
Şimşek, 2019[7]	M	68	yes	yes		yes	iohexol	110	CHD	CAG+PCI
Zhao, 2019[8]	F	71	yes		yes	yes	iopamidol	110	cerebral artery stenosis, CHD	cerebral magnetic resonance angiography (MRA)
Eleftheriou, 2018[9]	F	57	yes	yes			iodixanol	130	SAP	CAG+PCI
Heemelaar, 2018[10]	F	67	yes	yes			iodixanol	100	UAP	CAG
Hirata, 2018[11]	M	75		yes			iopamidol	-	STEMI	CAG+PCI
Kahyaoğlu, 2018[12]	M	66					iohexol	250	right common iliac artery 100% obstruction	Lower extremity angiography and stent
Dattani, 2018[13]	M	76	yes	yes			iohexol	120	CHD	CAG
Mardi H, 2017[14]	M	62	yes				iohexol	200	CHD	CAG
wangXF, 2016 [15]	F	55					-	-	Carotid artery stenosis	CAS
Zhao W, 2016[16]	M	61	yes	yes			-	-	Carotid artery stenosis	CAS

Study/year	gender	age	HT	DM	TIA/OCI	CKD	Contrast	Contrast Volume (ml)	diagnose	procedure
Li JR, 2016[17]	M	67	yes	yes			iohexol	-	ACI	cerebral angiography
	M	78					iohexol	-	Carotid artery stenosis	CAS
Spinal. 2016[18]	M	65	yes				iopromide	110	CHD	CAG
Li JT, 2015[19]	F	58	yes				iodixanol	90	Carotid artery stenosis	cerebral angiography
Raju G, 2015[20]	F	44	yes	yes		yes	iohexol	190	CHD	PCI
Li W, 2014[21]	M	64	yes	yes			iopromide	180	UAP	PCI
	M	75		yes			iopromide	150	STEMI	PCI
	M	88	yes				iopromide	200	STEMI	PCI
	F	70	yes				iopromide	230	UAP	PCI
	M	73	yes	yes			iopromide	300	STEMI	PCI
Xie CY, 2014[22]	M	84	yes				iodixanol	70	ACS	PCI
Wang J, 2014[23]	M	64	yes				iohexol	-	CABG-Carotid artery stenosis	CAS
Sun SJ, 2014[24]	M	75		yes			iopromide	150	NSTEMI	PCI
	M	88					iodixanol	150	UAP	PCI
	M	89	yes	yes			iodixanol	300	UAP	PCI
	M	74	yes				iodixanol	350	NSTEMI	PCI
	M	78		yes			iodixanol	210	UAP	PCI
	M	61	yes				iodixanol	50	CHD	PCI
	F	69		yes		yes	iopromide	150	UAP	PCI
	M	83		yes			iopromide	250	UAP	PCI
Kocabay, 2013[25]	M	68	yes				iopromide	250	UAP	PCI
	M	47	yes				iopromide	150	STEMI	PCI
	M	70		yes			iopromide	120	STEMI	PCI

Study/year	gender	age	HT	DM	TIA/OCI	CKD	Contrast	Contrast Volume (ml)	diagnose	procedure
	F	58	yes				iopromide	220	SAP	PTCA
	M	70	yes				iopromide	130	UAP	PCI
	M	63	yes				iopromide	280	STEMI	PCI
	M	68	yes	yes			iopromide	180	SAP	PCI
	M	72	yes				iopromide	140	SAP	CAG
	M	65	yes				iopromide	130	SAP	PCI
Ganiga SS, 2014[26]	M	63	yes	yes			iopromide	250	UAP, CABG	PCI
Adnan S, 2014[27]	M	70	yes			yes	iopromide	75	CHD	CAG
Liao.MT, 2013[28]	F	76	yes	yes			ioversol	150	UAP	PCI
Susan L, 2012[29]*	F	69	yes	yes			iodixanol	320	UAP, CABG	CAG
	F	68	yes	yes			-	-	UAP, CABG	CAG
Potsi S, 2012[30]	F	71	yes		yes		iopromide	25	Carotid artery stenosis	Carotid arteriography
Li JY, 2012[31]	F	70					iopamidol	300	UAP	PCI
Chisci.E, 2011[32]	F	76	yes	yes	yes	yes	iodixanol	300	UAP, CABG	PTCA+CAS
Akhtar.N, 2011[33]	M	39					iopamidol	80	UAP, CABG	CAG
Gure, 2011[34]	M	69					iohexol	100	ACS	PCI
Wilczewska, 2010[35]	F	70					-	-	UAP	PCI
BN ALP, 2009[36]	M	56	yes				iohexol	220	UAP, PCI, CABG	PCI
Borghi, 2008[37]	M	73	yes				iomeprol	320	UAP	PCI
González, 2008[38]	F	70	yes				-	1500	UAP	PTCA
Raja A, 2007[39]	F	-					iohexol	120	AMI	PCI
Yazici.M, 2007[40]	F	70	yes	yes			iobitridol	75	UAP	CAG
Tatli, 2007[41]	F	52					iomeprol	150	SAP	CAG

Study/year	gender	age	HT	DM	TIA/OCI	CKD	Contrast	Contrast Volume (ml)	diagnose	procedure
Yue XH, 2007[42]	F	75	yes				iohexol	-	cerebral artery stenosis	Cerebral artery stenting
Danenberg, 2006[43]	M	73					-	240	ACS	PCI
Velden J, 2003[44]	F	82	yes			yes	iomeprol	500	UAP	PCI
Gellen.B, 2003[44]	M	52	yes			yes	iopamidol	400	UAP, CABG	CAG
Yildiz A, 2003[45]	M	63					iomeprol	450	CHD	CAG
Merchut MP, 2002[46]	F	74	yes			yes	iopamidol	415	Renal artery stenosis	Renal arteriography
Dorothy JR, 2002[47]	F	63	yes	yes			iopromide	160	CABG, UAP	CAG
Zwicker JC, 2002[48]	F	52	yes			yes	ioversol	280	CHD	PCI
Dangas G, 2001[49]	M	82	yes				ioxaglate	230	CHD, carotid artery stenosis	CAS
Kwok BW, 2000[50]	M	53					ioversol	100	CHD	CAG
Vranckx.P, 1999[51]	M	68	yes	yes			iohexol	180	CABG, AMI	CAG
Sharp.S, 1999[52]	F	73	yes				diatrozoate	800	UAP	PCI
Sticherling C, 1998[53]	M	55					iomeprol	280	CABG, UAP	CAG
Antonellis J, 1996[54]	M	58	yes				iomeprol	260	CABG, UAP	CAG
	M	64					iomeprol	400	CABG, UAP	CAG
Muruve, 1996[55]	M	49	yes			yes	diatrozoate	700	UAP	PCI
Kamata.J, 1995[56]	M	62	yes				iopamidol	170	CABG, UAP	CAG
Rama BN, 1993[57]	M	59	yes				ioversol	370	AMI	PTCA
	M	45	yes				ioversol	190	OMI, UAP	PTCA
	M	68	yes				ioversol	262	UAP	PTCA
Parry R, 199[35]8	M	62	yes				iopamidol	270	CHD	CAG

KinnRM,1991[59]	M	55					diatrozoate	228	CABG, UAP	CAG
	M	61					diatrozoate	210	CABG, UAP	CAG
Utz.R,1988[60]	F	74	yes			yes	diatrozoate	250	Renal artery stenosis	Abdominal aortography
Haley EC J, 1984[62]	M	70	yes				diatrozoate	56	carotid artery stenosis	Carotid arteriography
	M	74		yes			diatrozoate	48	carotid artery stenosis	Carotid arteriography
Fischer, 1970[63]	F	56	yes				diatrozoate	60	UAP	CAG

Note: *recurrent cases.

Abbreviations: F, female; M, male. HT, hypertension. DM, diabetes mellitus. OCI, old cerebral infarction. TIA, transient cerebral ischemia. CKD, chronic kidney disease including renal impairment or patients who needed renal dialysis. CHD, coronary heart disease. AMI, acute myocardial infarction. AP, angina petites. unstable angina petites. SAP, stable angina petites. ACI, acute cerebral infarction. TIA, transient cerebral ischemia. CAG, Coronary angiography. PTCA, percutaneous coronary balloon dilatation. PCI, percutaneous coronary intervention. CABG, coronary artery bypass graft. CAS, carotid artery stent.

Table s1 The baseline data of all the cases included

Study/year	Coma (severe neurological symptoms)	syncope	cortical blindness	ophthal-moplegia	seizures	Hemiplegia, prosopoplegia	Delirium Confusion	nonspecific symptoms	Onset-time	duration	treatment	Complete resolution
Harada, 2020 [2]							Yes		Immediately	48h	Supportive care	yes
Lei, 2020[3]*					Yes			Yes	20h	4d	Supportive care	yes
					Yes			Yes	2h	6h	Supportive care	yes
Neilan, 2019 [4]		Yes						Yes	90min	48h	Supportive care	yes
Renault, 2019[6]							Yes	Yes	15min	6d	Anticonvulsive medication	yes
Defalco, 2019[7]			Yes		Yes			Yes	6h	7d	Supportive care	yes
Şimşek, 2019[8]					Yes				4h	60h	Antiepileptic medication	yes
Zhao, 2019[9]#	Yes								10min	56d	CPR, intubation, ventilation	No(die)
Eleftheriou, 2018[10]					Yes			Yes	27h	5d	antiepileptic medication	yes
Heemelaar, 2018[11]	Yes								minutes	58h	Intubation, ventilation	yes
Hirata, 2018[12]	Yes							Yes	□-	12d	Intubation, ventilation	yes
Kahyaoğlu, 2018[13]					Yes				1h	24h	hydration and sedative medication	yes
Dattani,2018[14]			Yes				Yes	Yes	90min	9d	Supportive care	yes
Mardi H,2017[15]			Yes						Immediately	48h	Supportive care	yes
wangXF,2016 [16]							Yes	Yes	40m	6d	Supportive care	yes
Zhao W,2016[17]	Yes				Yes			Yes	5h	5d	Supportive care	yes
Li JR,2016[18]					Yes				4h	48h	Supportive care	yes
					Yes				18h	72h	Supportive care	yes
Spinal.2016[19]							Yes		minutes	24h	Supportive care	yes

Study/year	Coma (severe neurological symptoms)	syncope	cortical blindness	ophthal-moplegia	seizures	Hemiplegia, prosopoplegia	Delirium Confusion	nonspecific symptoms	Onset-time	duration	treatment	Complete resolution
Li JT,2015[20]	Yes							Yes	30min	5d	Supportive care	yes
Raju.G,2015[21]					Yes	Yes			Few hours	72h	Anticonvul-sants, hemodialysis	yes
Li W,2014[22]			Yes						2h	14h	Supportive care	yes
								Yes	18h	25h	Supportive care	yes
							Yes	Yes	13h	15h	Supportive care	yes
							Yes		immediately	5h	Supportive care	yes
								Yes	20min	3h	Supportive care	yes
Xie CY,2014[23]							Yes		1h	10h	Supportive care	yes
Wang J, 2014[24]#					Yes		Yes		2h	15d	Supportive care	No(right hand muscle strength decline)
Sun SJ, 2014[25]							Yes		18h	7h	Supportive care	yes
								Yes	13h	23h	Supportive care	yes
							Yes		0.3h	1.5h	Supportive care	yes
							Yes		22h	27h	Supportive care	yes
							Yes		5h	19h	Supportive care	yes
							Yes		0.2h	5h	Supportive care	yes
								Yes	23h	12h	Supportive care	yes
								Yes	15h	26h	Supportive care	yes
G.Kocabay, 2013[26]						Yes			4h	12h	Supportive care	yes
							Yes	Yes	1h	8h	Supportive care	yes
							Yes	Yes	1h	12h	Supportive care	yes

Study/year	Coma (severe neurological symptoms)	syncope	cortical blindness	ophthal-moplegia	seizures	Hemiplegia, prosopoplegia	Delirium Confusion	nonspecific symptoms	Onset-time	duration	treatment	Complete resolution
#				Yes					0.5h	—	Supportive care	No (blepha-roptosis, diplopia)
							Yes		2h	14h	Supportive care	yes
							Yes	Yes	0.5h	10h	Supportive care	yes
				Yes					1h	30h	Supportive care	yes
							Yes	Yes	3h	12h	Supportive care	yes
								Yes	2h	16h	Supportive care	yes
Ganiga.S.S, 2014[27]			Yes						0.5h	72h	Supportive care	yes
Adnan.S, 2014[28]							Yes	Yes	3h	Seveal hours	dialysis	yes
Liao.M.T, 2013[29]			Yes			Yes			immediately	48h	Supportive care	yes
Susan.L,2012[30]*					Yes	Yes		Yes	12h	7d	intravenous ben-zodiazepines, thrombolysis	yes
					Yes	Yes			-	-	Supportive care	yes
Potsi S,2012[31]						Yes	Yes		immmedi-ately	4d	Supportive care	yes
Li JY,2012[32]							Yes	Yes		5h	Supportive care	yes
Chisci.E,2011[33]	Yes					Yes			Immediately	48h	intravenous mannitol, meth-ylprednisone	yes
Akhtar.N, 2011[34]			Yes						immediatly	1h	Supportive care	yes
Gure,2011[35]						Yes	Yes	Yes	0.5h	6h	Supportive care	yes
Wilczewska, 2010[36]				Yes	Yes				-	72h	Supportive care	yes
BN ALP, 2009[37]			Yes						72h	4d	Supportive care	yes

Study/year	Coma (severe neurological symptoms)	syncope	cortical blindness	ophthal-moplegia	seizures	Hemiplegia, prosopoplegia	Delirium Confusion	nonspecific symptoms	Onset-time	duration	treatment	Complete resolution
Borghi, 2008[38]			Yes					Yes	shortly	24h	Supportive care	yes
González, 2008[39]								Yes	-	24h	Supportive care	yes
Raja A,2007[40]							Yes		-	48h	Supportive care	yes
Yazici.M,2007[41]			Yes					Yes	-	72h	Supportive care	yes
Tatli,2007[42]			Yes					Yes	45min	5h	Supportive care	yes
Yue XH,2007[43]							Yes	Yes	immediately	72h	Supportive care	yes
Danenberg, 2006[44]			Yes						2h	7h	Supportive care	yes
Velden J,2003[45]					Yes	Yes			30m	40h	Supportive care	yes
Gellen.B, 2003[46]			Yes					Yes	30m	72h	Supportive care	yes
Yildiz A,2003[47]							Yes		immediately	12h	Intravenous dexamethasone	yes
MerchutMP, 2002[48]				Yes				Yes	1d	4d	Supportive care	yes
Dorothy.JR, 2002[49]			Yes						immediately	5d	Supportive care	yes
Zwicker JC, 2002[50]			Yes					Yes	2h	36h	Supportive care	yes
Dangas G, 2001[51]						Yes	Yes		immediately	48h	Supportive care	yes
Kwok BW, 2000[52]			Yes					Yes	30m	12h	Supportive care	yes
Vranckx.P, 1999[53]#			Yes	Yes				Yes	45m	6d	CPR, temporary transvenous pacemaker	No (Forget-ting and vision loss)
Sharp.S, 1999[54]					Yes	Yes				24h	Intubation and ventilation, ben-zodiazepines	yes
SticherlingC, 1998[55]			Yes						10min	5d	Supportive care	yes

Study/year	Coma (severe neurological symptoms)	syncope	cortical blindness	ophthal-moplegia	seizures	Hemiplegia, prosopoplegia	Delirium Confusion	nonspecific symptoms	Onset-time	duration	treatment	Complete resolution
Antonellis J, 1996[56]			Yes							32h	Intravenous dexamethasone	yes
			Yes							30h	Intravenous dexamethasone	yes
Muruve, 1996[57]					Yes					48h	Hemodialysis, anticonvulsants	yes
Kamata.J, 1995[58]			Yes							48h	Supportive care	yes
RamaBN, 1993[59]			Yes					Yes	30min	12h	Supportive care	yes
			Yes					Yes	mins	24h	Supportive care	yes
				Yes					1h	15min	Supportive care	yes
Parry R, 1993[60]			Yes							72h	Supportive care	yes
KinnRM,1991[61]			Yes							24h	Supportive care	yes
			Yes							36h	Supportive care	yes
Utz.R,1988[62]			Yes			Yes			30h	5w	dialysis	yes
Haley EC J, 1984[63]							Yes	Yes	immediately	8d	Supportive care	yes
							Yes		hours	48h	Supportive care	yes
M.Fischer, 1970[64]			Yes						-	18h	Supportive care	yes

Note:* the recurrent cases.

Abbreviations :F for female,M for male. HT,hypertension.DM, diabetes mellitus .OCI, old cerebral infarction. TIA, transient cerebral ischemia. CKD, chronic kidney disease including renal impairment or patients who needed renal dialysis. CHD, coronary heart disease. AMI, acute myocardial infarction. AP, angina petites. unstable angina petites. SAP, stable angina petites. ACI, acute cerebral infarction. TIA, transient cerebral ischemia. CAG, Coronary angiography. PTCA, percutaneous coronary balloon dilatation. PCI,percutaneous coronary intervention .CABG, coronary artery bypass graft. CAS,carotid artery stent. H for hours, min for minutes, d for days, w for weeks.