

Neurotoxicity Associated with Radiological Contrast Agents Used during Coronary Angiography: A Systematic Review

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Abstract Contrast media enhances the visualization of the anatomic structures in radiological studies, allowing internal tissues such as blood vessels, kidney, ureters, adrenals and other organs to be identified. The evolution of contrast media highlights the efforts to develop less toxic chemical agents that possess low viscosity and osmolality. However, adverse effects such as idiosyncratic reactions, and organ specific damage are well characterized. Neurotoxicity, an important and dose related effect, appears to be due to disruption of the blood-brain-barrier by the high osmolality of the contrast agent. From devastating cortical blindness to paralysis and seizures, an array of neurological manifestations has been described. In this systematic review, we describe the contrast-induced neurologic injury following coronary angiography and discuss the proposed mechanisms of injury leading to neurotoxicity.

Keywords: neurotoxicity, iodinated contrast media, blood-brain barrier, neurological injury, coronary angiography, cardiovascular risk factors, types of contrast agents

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1. Introduction

Iodinated contrast media were deemed safe to use in humans in the 1920s and its first application was for a carotid angiogram performed in 1927. Over the past century, the chemical composition of contrast agents has been refined to be less toxic with the development of low-osmolality and low viscosity non-ionic alternatives. Although contrast agents have revolutionized radiographic diagnostic testing, their associated adverse effects can hinder their utility [1]. Common adverse effects of intravenous contrast administration include idiosyncratic reactions such as anaphylaxis, generalized weakness, nausea and hypotension. There are also dose-related effects on specific organ-systems of which contrast-induced nephropathy is the most well-known. However, reactions involving the nervous system occur more frequently, exceeded only by the incidence of those involving the cardiovascular system [1,2,3,4].

Studies have shown that ionized contrast agents can severely alter neuronal function when introduced directly

into the nervous system [2]. Yet, contrast induced neurologic injury is not a well understood entity and is often undiagnosed. The majority of existing literature on this subject only describes contrast induced central nervous system (CNS) injury associated with cerebral arteriography and arch aortography. In this paper we conduct a systematic review of case reports describing contrast induced neurologic injury following coronary angiography.

Contrast induced adverse reactions associated with the nervous system are usually dose related [2]. Although the exact mechanism of contrast induced CNS damage is poorly elucidated, several possible explanations have been proposed. Contrast agents can have both excitatory and inhibitory influences on neurons. Hyperosmolality of certain contrast agents can disrupt the blood-brain barrier (BBB) by drawing water out of brain capillary endothelial cells, causing shrinkage of cells and separation of tight junctions. This separation of tight junctions is compounded by increased intraluminal tension that occurs due to the vasodilatory effects of the contrast agent and also from the high pressure of the contrast injection [2,3,5,6,7,8,9]. There appears to be greater disruption of

the BBB with contrast agents as compared with intravenous mannitol of equivalent osmolarity, thus demonstrating that there exist other intrinsic properties of contrast agents which contribute to this disruption apart from hyperosmolarity [2,10,11]. Areas of the brain which are not protected by the BBB such as certain regions in the hypothalamus and the area postrema may be more susceptible to the effects of contrast agents from exposure to higher concentrations in the blood [12,13]. The extent of disruption also appears to be related to the duration of injection. It is important to remember that disease states like certain infections increase permeability of the BBB and in such states, contrast agents enter the brain more easily, predisposing to further injury [2,14,15].

A broad spectrum of neurological sequelae secondary to contrast administration can occur. These range from the benign to the serious and include nausea, vomiting, vasovagal reactions, headache, seizures, cortical blindness, spinal cord ischemia, cortical edema and focal neurological deficits. Nausea and vomiting are mediated by the irritant effect of contrast agents on the area postrema of the medulla [2,14]. Hypotension may be potentiated by its vasodilatory properties [15,16]. Vasovagal reactions including bradycardia, hypotension and rarely apnea and asystole are mediated by receptors found in the extra-cerebral segment of the internal carotid artery and the external carotid artery [16]. Symptoms of generalized malaise and fatigue may be due to rapid flux of fluid across compartments induced by the hyperosmolarity of the contrast agent. Areas unprotected by the BBB are especially susceptible to such rapid fluid shifts and can sometimes result in seizures. Up to 6% of patients with brain metastasis develop seizure following radio contrast studies. Such reactions occur more frequently with the administration of ionic as compared with non-ionic contrast agents [2,15]. Patients with preexisting arterial disease are at an increased risk for transient brain and spinal cord ischemia, caused by momentary blood displacement by the contrast agent injection. Moreover, the delayed passage of contrast dye through stenosed and calcific vasculature in the brain and spinal cord potentially increases its toxic effects. The risk of spinal cord injury with aortography was estimated at 0.2% in 1957 [17] and is further augmented with a more distal aortic occlusion [18,19]. Manifestations of spinal cord toxicity include weakness, paresthesias and myoclonus. These may develop as late as eighteen hours after the angiographic procedure. Imaging may show cord edema, central hemorrhage, central liquefaction and degenerative changes in the ascending and descending white matter tracts [20,21,22]. Transient cortical blindness has been reported in 0.3-1% of vertebral arteriograms and is thought to result from direct neurotoxicity of the contrast agent on the occipital cortex. This may be accompanied by vertebrobasilar dysfunction including pupillary and oculomotor disturbances, formed hallucinations and memory loss. Symptoms may resolve spontaneously over hours to days but residual defects may persist [23,24,25,26]. Computed tomography imaging may reveal persistence of contrast in the occipital cortex [27]. The incidence of focal neurological deficits post-catheter cerebral arteriography is reported at 0.5-12%. However, this is thought to be due to the ischemic complications of the catheterization procedure rather than

the toxic effects of the contrast agent itself [2,24]. Fatal cortical edema as a complication of arteriography has been reported in the literature and has been attributed, at least in part, to osmotic BBB compromise.

2. Methods

Multiple databases including PubMed, Google Scholar, CINAHL, Cochrane Central and Web of Science were queried for studies with keyword searches including “contrast induced central nervous system damage, coronary angiography and contrast induced neuropathy” was done on May 6th, 2019. Case reports and case series describing adverse CNS effects associated with contrast administration during coronary angiography were identified and appraised. The bibliography of each relevant publication was then reviewed for relevant data. Extracted data from each case report when available included type of contrast used, total dose of contrast, age of the patient, presence of hypertension, diabetes and hyperlipidemia, indication for coronary catheterization, reported neurological sequelae, time of onset of symptoms, supportive imaging, pretreatment and treatment.

3. Result

A total of 33 publications of case reports and case series were identified, altogether comprising 75 patients who had undergone coronary angiography. 36% (n=27) were female and 64% (n=47) were male. The patient ages ranged from 16 to 82 years with a median age of 59 years. The most common indications for the procedure were angina (40%) and STEMI (7%). 28% of cases did not specify an indication. Medications administered prior to the procedure were infrequently reported (reported in 10 cases) and included aspirin, clopidogrel, heparin drip, one case of N-acetyl cysteine and intravenous saline infusion for renal protection and one case of prednisone and antihistamine given for a prior history of contrast allergy. Cardiovascular risk factors were inconsistently reported as follows: diabetes was reported in 14 patients (18%), hypertension in 26 patients (34%) and hyperlipidemia in 8 patients (10%). Cortical blindness occurred in 36% of patients with reported diabetes, in 42% of patients with reported hypertension and in 25% of patient with reported hyperlipidemia. 37% of patient with reported hyperlipidemia experienced confusion. Overall, cortical blindness was the most common adverse reaction, reported in 44 cases (58%). Altered mental status was the second most common adverse effect, documented in 18 patients (24%), of which 1 patient required intubation for airway protection. Seizures were reported in 4 cases (5%). Headache was reported in 5 cases (7%). Spinal myoclonus was observed in 1 case (1%). There were 5 documented cases of limb paralysis or weakness (7%) and 1 case of coma (1%).

13 types of contrast agent were used. 27% (19 cases) used Iopaque cornar (metrizoat), 16% (11 cases) used Iopromide, 11% (8 cases) used Omnipaque (iohexol), 10% (7 cases) used Optitray 350 (ioversol), 7% (5 cases) used Xenetix 350 (iobitridol), 6% (4 cases) used Imeron

(iomeprol) , 4% (3 cases) used Hexabrix, 3% (2 cases) used Iodixanol, 3% (2 cases) used opopromide and 1% (1 case) each used Ultravist 370 or isovue or iopamidol or Visipaque. The type of agent used was not specified in 5 cases (7%).

Complete or partial cortical blindness was reported in 100% (n=11) cases for Isopaque cornar (metrizoat). No other side-effects were reported. In most cases symptoms appeared within 6 hours of administration (onset ranging from 1 to 30 hours). Contrast dose ranged from 80 to 155 ml. Doses did not correlate with severity of cortical blindness (complete versus partial) and also did not correlate with symptom onset.

Altered mental status was the most common CNS side-effect of Iopromide (n=8), comprising of 5 cases (45%). Other reported side-effects included ophthalmoplegia in 2 cases (18%), aphasia in 1 case (9%), cerebellar dysfunction in 1 case (9%) and cortical blindness in 1 case (9%). Contrast dose ranged from 120 to 280 ml and did not correlate with symptom onset.

In the 8 cases which used Omnipaque (iohexol), cortical blindness was the most common CNS side effect, reported in 4 cases (50%). There were 2 cases (25%) of altered mental status, 1 case (12%) of spinal myoclonus, 1 case (12%) of hypotension and 1 case (12%) of focal weakness. Contrast dose ranged from 100 to 190 ml and

did not correlate with symptom onset. Symptoms began between 2 to 94 hours, usually occurring after 24 hours of contrast administration.

Altered mental status and cortical blindness were the most common side-effects reported with Optitray 350 (ioversol) (n=7) with 3 cases (43%) each. There was 1 case (14%) of homonymous hemianopsia. Contrast dose ranged from 100 to 262 ml and did not correlate with symptom onset. Symptom onset ranged from 15 minutes to 48 hours, usually occurring after 24 hrs.

Altered mental status was the most common CNS side effect of Xenetix 350(iobitridol) (n=5) described in 4 cases (80%) followed by headache which was reported in 3 cases (60%). Seizures, limb paralysis, amnesia and cortical blindness were reported in 1 case each (20% each). Contrast dose ranged from 75 to 700ml and did not correlate with symptom onset. Symptom onset occurred within hours to 15 days post-procedure.

Amnesia was the most common CNS side effect of Imeron (iomeprol) (n=4), reported in 3 cases (75%). Other side effects included headache as reported in 2 cases (50%), extremity numbness in 2 cases (50%), cortical blindness and altered mental status in 1 case (25%) each. Contrast dose ranged from 320 to 500 ml and did not correlate with symptom onset, which ranged from 24 hours to 5 days post-procedure.

Table 1. Adverse Reactions and Imaging

Side Effect	Imaging
Transient Cortical Blindness, mild headache [30]	CT wnl
Complete cortical blindness, retrograde amnesia [31]	CT: pronounced intracerebral enhancement of contrast media in the posterior third of the brain without evident relation to a vascular territory
Cortical blindness, agitation, confusion, dysarthria, alkalulia, apraxia, anosognosia [35]	CT: intense gyral enhancement of the right occipital lobe involving cortical as well as subcortical areas
Cortical blindness, confusion [36]	MRI: bilateral, predominantly right-sided ischemia in the territory of the posterior cerebral arteries, with no extravasation of contrast media. Both posterior cerebral arteries as well as the basilar artery were patent on MR angiography
Cortical blindness, headache, confusion, retrograde amnesia, hypertensive emergency [37]	CT: marked bilateral contrast enhancement in the occipital lobes and no evidence of cerebral hemorrhage
Cortical blindness [40]	CT: marked bilateral contrast enhancement in the occipital lobes and no evidence of cerebral hemorrhage.
Cortical blindness, confusion, retrograde amnesia [42]	CT: marked bilateral hyperdense area in a symmetric distribution in the occipital lobes due to retention of the contrast agent used during angiography. 6hrs after no abnormalities found. MRI: unremarkable other than age/risk factor related, long-standing mild ischemic changes
Cortical blindness [43]	CT, MRI wnl
Cortical blindness [43]	MRI wnl
Cortical blindness nausea, vomiting, headache [44]	CT wnl
Cortical blindness [52]	CT, MRI wnl
Cortical blindness [58]	MRI: occipital contrast staining, indicating CIN
Seizure [38]	CT: hyperdensity of cerebral sulci in the right frontal area, indicative of a diffuse subarachnoid hemorrhage, without an apparent source of bleeding
Seizure, left-sided homonymous hemianopia, hemisensory loss, hemiparesis, and hemineglect. [45]	CT: sulcal effacement in the right cerebral hemisphere due to cerebral swelling, markedly in the high frontal and parietal lobes
Seizure [50]	CT: hyperdensity in the right frontoparietal region consistent with intracerebral bleed, MRI: wnl
Seizure, confusion, tonic deviation [55]	CT: Regional gyri hyperdensity
Spine MRI [54]	Spine MRI wnl
Unresponsiveness, preceded by hyperventilation, disorientation and somnolence [32]	CT: pronounced brain atrophy and an arachnoidal cyst, but was otherwise wnl
Unresponsiveness, left-sided hypertonia of the arm, bilateral pathological plantar reflex [59]	CT: right-sided hypodensities in the watershed regions, suggestive of ischemia, which did not fully explain the neurological state CTA: normal basilar artery, excluding brain stem stroke
Amnesia, headache and right upper extremity numbness. [33]	CT: abnormal contrast enhancement at the right frontal, occipital and parietal cortical areas. Left cerebral hemisphere was normal
Amnesia, disorientation, drowsiness, Malignant hypertension, aphasia, right side hemiparesis [34]	CT: hyperdense material filling the sulci of both brain hemispheres
Headache, left sided weakness [51]	CT: extensive intravascular contrast with cortical staining, primarily over the right cerebral hemisphere and left cerebral hemisphere watershed territories
Agitation, confusion [55]	CT: Subarachnoid hyper-attenuation, cerebral edema
Agitation, headache [55]	CT: Cortical intravascular contrast staining

Table 2. Contrast and Adverse Reactions [28-59]

Contrast Type	Number of Cases	Dose	Adverse Reaction	Onset
Isopaque cornar (metrizoat)	19	80 -155 ml	All partial or complete cortical blindness	Most within 6 hr; range: 1-30 hr
Omnipaque (iohexol)	8	100ml	Disorientation	
		120ml	Agitation, confusion, convulsion, slurred speech, decreased GCS	18 hr
		110ml	Spinal myoclonus	72 hr
		170ml	Cortical blindness	24 hr
		190ml	Headache, left sided weakness	72 hr
		160ml	Cortical blindness, dull headache and hypotension	24 hr
		45ml	Partial cortical blindness	2-3 hr
Hexabrix	3	220ml	Cortical blindness	96 hr
		200ml	Complete cortical blindness, severe headache	48 hr
		260ml	Transient Cortical Blindness, mild headache	32 hr
		400ml	Transient Cortical Blindness, mild headache, vomiting, confusion	30 hr
Iomeprol (imeron)	4	280ml	Complete cortical blindness, retrograde amnesia	5 days
		450ml	Transient partial amnesia, headache and right upper extremity numbness	
		500ml	Disorientation, drowsiness, hypertensive emergency, aphasia, right side hemiparesis, retrograde amnesia	40 hr
		320ml	Severe headache, cortical blindness, hypertensive emergency	24 hr
Ioversol (Optitray 350)	7	145ml	Severe physical and verbal agitation	24 hr
		130ml	Hyperventilation, disorientation	12 hr
		150ml	Consciousness disturbance, global aphasia, cortical blindness, and right-sided weakness	48 hr
		100ml	Cortical blindness, catatonia	12 hr
		167ml	Cortical blindness	24 hr
		220ml	Cortical blindness	12 hr
		262ml	Homonymous hemianopsia	15 min
Ultravist 370	1	135ml	Agitation, confusion, cortical blindness, dysarthria, acalculia, apraxia, anosognosia	
Iobitridol (xenetix 350)	5	75ml	Cortical blindness, headache, confusion, retrograde amnesia, hypertensive emergency	72 hrs
		700ml	Confusion, seizure, tonic deviation	
		100ml	Confusion, agitation	15 days
		75ml	Agitation, headache	within hours
		190ml	Headache, hemiplegia	72 hrs
		1500ml		
Not specified	5	1500ml	Seizure	
			Disorientation (GSC6) left-sided hemiplegia and positive Babinski's sign of her left foot, hypertension, monoplegia	10 days
		240ml	Cortical blindness	7 hr
		100ml	Cortical blindness	48 hr
		100ml	Cortical blindness	24 hr
Iopromide	11	120-280 ml	5 confusion, 1 aphasia, 2 monoplegia, 2 ophthalmoplegia, 1 cerebellar dysfunction, 1 cortical blindness.	variable
Iodixanol 320 mgI/mL	2	320ml	Seizure, left-sided homonymous hemianopia, hemisensory loss, hemiparesis, and hemineglect	12 hr
		100ml	Unresponsive to verbal commands and painful stimuli, hypertonia of left upper extremity, bilateral pathological plantar reflex	
Isovue	1	150m	Seizure	
Iopamidol	1	80ml	Cortical blindness	1 hr
Iopopromide	2	205ml	Confusion, decreased GCS	12 hr
		100ml	Cortical blindness	24 hr
		440ml	Cortical blindness	5 days

The only reported CNS side effect of Hexabrix was cortical blindness, in 3 cases (100%). Contrast dose ranged from 200 to 400ml and did not correlate with symptom onset, which ranged from 30 to 48 hours post-procedure.

Both cases of Iodixanol (320 mgI/mL) were associated with grave CNS side-effects including generalized seizure,

limb paralysis and coma. Contrast doses were 100 ml and 320 ml. Symptom onset was reported in only one case, precipitating the seizure 12 hours post-procedure.

Iopopromide was associated with 2 cases of altered mental status and cortical blindness, symptom onset occurring 12 to 24 hours post-procedure. Contrast dose used were 205 ml and 100 ml respectively.

The one case using 135 ml of Ultravist 370 was associated with altered mental status, cortical blindness, dysarthria, parapraxia and anosognosia. 150 ml of Isovue use in a case was associated with generalized seizure. The use of Iopamidol 80 ml was associated with cortical blindness with symptom onset 1 hour after contrast administration. The one case using Visipaque was associated with cortical blindness (dose= 440ml) with symptom onset at 5 days post-contrast administration. [28-59]

Imaging: Computed tomography or magnetic resonance imaging results were reported in twenty-eight cases. Imaging was most commonly utilized in cases of cortical blindness (12 cases). The most common finding was abnormal contrast enhancement in the occipital lobe (6 cases). A normal report was seen in five cases. One case documented ischemia in the posterior circulation. Imaging was performed for four cases of seizures, three of which revealed a hemorrhage and one of which revealed cerebral edema. Imaging was reported for 1 case of myoclonus, where MRI of spine was unrevealing. [28-59]

Treatment: Treatment was documented for sixteen cases including agitation, seizure, cortical blindness and altered mental status and consisted of symptomatic and supportive measures with the exception of one case which required intubation for seizures and airway protection.

4. Discussion

Diverse neurological sequelae of intravenous contrast administration have been reported in literature. However, the data on the mechanism of injury remains scarce and largely ambiguous. The literature that does exist attributes the neurotoxic effects due to direct toxicity on the brain or spinal cord parenchyma and induced hematological and vascular changes. High concentrations of contrast cause red blood cell aggregation and thereby occlusion of cerebrovascular territories [22,60]. Despite the aggregation of red cells and increased viscosity, cerebral blood flow is somewhat increased following carotid arteriography, probably secondary to a direct vasodilatory effect of the contrast agent [8]. This assertion has been supported by experimental animal experiments but has not been validated in humans [2,7]. Research on spinal contrast toxicity suggest two potential mechanism of injury - of neuro-excitation associated with the contrast agent's intrinsic chemical composition and of inhibition associated with its hypertonicity. [2,18]. It has been speculated that contrast-induced neuronal injury may be dose related and worsens with repeated contrast administration. [2]

Transient cortical blindness (TCB) has been reported to complicate 0.3 to 1% of vertebral arteriograms [23,24,25] but has never been studied in context of coronary catheterization. TCB may be complete or incomplete but invariably involves both homonymous fields. [2] The results of our analysis show that cortical blindness was

the most common neurologic adverse event seen with intravenous contrast administration, present in 58% of all reviewed cases. The onset time of TCB however did not correlate with total contrast dose. Consistent with what

has previously reported, most patients experienced complete recovery over hours to days. TCB was also the most common neurological side effect in patients with cardiovascular risk factors of HTN, HLD and DM.

Analysis of the results of imaging studies, though infrequently available, revealed a consistent finding of abnormal contrast enhancement of the occipital lobe, associated with the cases of TCB. Contrast persistence in occipital cortex of cases of TCB supports the hypothesis of direct toxicity as the etiology of this adverse effect [27]. Patients with TCB are often unaware of its presence and may not report symptoms, remaining undiagnosed unless the vision field is specifically tested. Thus, TCB is likely to be under-reported and may be even a more prevalent post-coronary angiography than our data reflect.

Altered mental status was the second most common neurologic adverse effect of intravenous contrast administration seen in our analysis and was observed in 24% of the reviewed cases. Other adverse effects seen in our analysis included limb paralysis, weakness, headache, seizure, myoclonus and coma. We found no overall correlation between total contrast dose and the onset or severity of the adverse effects. No specific imaging pattern was identified in relation to any of the adverse effects other than TCB.

Only a few of the cases reviewed stated the treatment offered to patients. Those that did, described a symptom-based approach with supportive therapies. Supportive treatment of neurological complications consists of systemic support, including blood pressure, temperature and electrolyte monitoring. [2] Anticonvulsants such as diazepam have been reported to be effective for persistent seizures following intravenous contrast agent administration in patients with brain metastases [61] as well as for contrast related myoclonus [29,62]. This current approach towards treatment of contrast related neurotoxicity is based upon the current understanding of its pathogenesis and anecdotal evidence. No clinical trials have been performed to substantiate this. Experimental studies in animal models have demonstrated that premedication with low molecular weight dextran and corticosteroids reduce the neurotoxic effects of contrast agents by prevention of red blood cell aggregation and decreasing osmotic permeability of the BBB. [63,64,65,66,67,68] however there is lack of evidence for this in human subjects. Avoidance of general anesthesia to monitor mental status and routine assessment of the visual fields after procedures involving contrast administration are some steps that can be undertaken to improve detection of these neurological adverse effects [2]. Extreme caution should be exercised in patients who are at an increased risk for contrast related neurologic injury. Patients such as those with a recent cerebral infarction should ideally have contrast exposure through cerebral and possibly coronary arteriography delayed for at least thirty days [2,9,11]. Patients with brain metastases are poor candidates for coronary intervention and may stand to benefit from pre-procedural diazepam prophylaxis to reduce the risk of seizures with intravenous contrast agent [61].

Although cumulative contrast dose limits have been proposed for cerebral angiography [62,69] such recommendations for coronary angiography are lacking. There is an urgent need for further research to establish

safe contrast dose limits in coronary angiography to prevent neurological adverse events. Our analysis demonstrates that most adverse events occurred with a cumulative contrast doses of 100cc or greater. However, adverse neurologic events at doses as low as 45 cc have been described.

5. Conclusion

Contrast agents have undoubtedly revolutionized and expanded the diagnostic reach of radiology in modern medicine. However, with their ever-increasing dependence and use it is only now that the entire spectrum of their adverse effect profile is being unmasked. Adverse reactions of contrast agents involving the nervous system occur more frequently than contrast induced nephropathy, nonetheless they remain largely under-detected, under reported and poorly understood. The existing literature only describes contrast induced CNS injury associated with cerebral arteriography and arch aortography. No systematic reviews of contrast induced neurotoxicity with coronary angiography have been published. Our review of 75 cases is the first systematic review describing contrast induced neurologic injury in context of coronary catheterization. Transient cortical blindness was the most common neurologic adverse effect overall (58% of all cases reviewed). It was also seen most commonly in patients with cardiovascular risk factors of hypertension, hyperlipidemia and diabetes. It was also the only adverse effect that correlated with a consistent imaging pattern of contrast agent persistence in the occipital cortex. Altered mental status was the second most common neurological adverse effect (24% of all cases reviewed) observed in our review. We found no correlation between total contrast dose and the onset or severity of neurological adverse reactions. Our review highlights the gaps in our current understanding of neurological adverse effects of contrast agents and supports the urgent need for further research in this field for the establishment of safety limits of contrast dosing in coronary arteriography for the overall safety of our patients.

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