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REVIEW ARTICLE

Thrombocytopenia Induced by Iodinated Contrast Media: A Systematic Review

Guerrero-Márquez Francisco José*[,1], Cubero-Gómez José Maria [2], Ropero-Luis Guillermo [3], Martin-Ramos Beatriz [3], Ruz-Zafra Aurora[3], Avilés-Toscano Alberto Luis [1], Cristobo-Sainz Pablo [4], Grana-Costa Mariela [3].

1. Department of Cardiology, Hospital La Serranía, Ronda, Malaga. Spain.
2. Department of Cardiology. Haemodynamic and Interventional Cardiology Unit, Virgen del Rocío University Hospital, Seville, Spain.
3. Internal Medicine Department, Hospital La Serranía, Ronda, Málaga. Spain
4. Department of Cardiology, Virgen del Rocío University Hospital, Seville, Spain.

* guerreromar24@gmail.com

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ABSTRACT

Iodinated contrast media are routinely used in clinical practice for diagnostic and therapeutic purposes. Adverse effects of their administration have an incidence of 3 %, and mostly consist of mild skin allergic reactions, with severe reponses such as anaphylaxis representing only 0.22 %. Contrast-induced thrombocytopenia is an extremely rare, underdiagnosed condition that most often occurs after infusion of hyperosmolar contrast agents, with low-osmolarity compounds being less likely the trigger. We report a systematic review of this condition based on the currently available series of case reports (18), as well as the clinical course of the presentation and platelet count during episodes. The physiopathogenic mechanism remains unknown, although the presence of some immune-mediated process involving changes in platelet aggregation and activation is currently accepted. Platelet response is immediate (within a few hours after exposure to the contrast agent) and consists of a fall in platelet count to < 20 x 10^9/L, which returns to normal at day 3 or 4. Diagnostic criteria are based on those by George and Arnold, the latter more specific for drug-induced thrombocytopenia. No routine diagnostic laboratory tests are presently available to establish a definite diagnosis, and treatment usually consists of support measures to prevent complications from occurring, but steroids, immunoglobulins, plasma exchange and/or platelet transfusions may be used. Despite its low incidence, iodinated contrast-induced thrombocytopenia is a complication to consider that may cause severe thrombocytopenia after administration of iodinated contrast agent during some diagnostic test and/or angiography.

Keywords: iodinated contrast media, thrombocytopenia, adverse effect.

INTRODUCTION

Iodinated contrast media are agents used visualize and/or improve structure or fluid characterization in tissues during medical exams in order to reach a diagnosis. Their radiopaque characteristics are useful for the study of various conditions across a number of specialties, including radiodiagnosis, cardiology, and vascular intervention. They were initially used for radiological diagnosis exclusively; however, over the years their use was extended to cover support for intervention with a number of procedures such as percutaneous coronary angiography and other structural interventions in the field of cardiology and other specialties. The molecular characteristics of contrast media have also evolved substantially aiming to reduce complications and/or adverse effects following administration. With early compounds, which were based on tri-iodobenzoic acid, adverse reactions amounted to 15 %, much higher than the currently observed 3 % with low-osmolarity agents.[1]

Non-complicated allergic reactions represent the commonest adverse effect characterized by the presence of wheals and/or other forms of skin rash associated with pruritus, they develop almost immediately after a first injection. On other occasions the reaction is less immediate, and the response to treatment with antihistamines and corticosteroids is unsatisfactory.[2] Rarer complications that are usually severe include thrombocytopenia, angioedema, ventricular arrhythmia or serious anaphylaxis, which may result in shock and patient demise.[3] Contrast-induced thrombocytopenia is a very rare condition, with case reports being exceptional since early use during the 1980s to this day.[4-18]

Iodinated contrast-induced thrombocytopenia

Contrast-induced thrombocytopenia is one of the so-called drug-induced immune thrombocytopenias, which cause a decrease in platelet count (< 30 x 10^9/L) because of destruction in peripheral blood or reduced production in the bone marrow.[19] Multiple drugs may induce this effect, including those used for chemotherapy, heparins, quinidine, tirofiban, abciximab, procainamide, protamine, and a number of monoclonal antibodies, among others. Iodinated contrast type substantially affects the likelihood of developing thrombocytopenia, which is higher with hyperosmolar contrast agents such as *iopanoic acid, diopromide, sodium amidotrizoate, sodium diatrizoate,* and *meglumine*.[20] Current hypoosmolar contrast media (*ioxaglate, iopamidol, iodixanol*) are less likely to induce thrombocytopenia as they reduce platelet activation and aggregation.[21] Figure 1 shows the differential characteristics of ionized versus non-ionized contrast media.

	Ionized contrast medium	Non-ionized contrast medium
Elimination renal	90%	95%
Advantages	Low incidence nephrotoxicity	– Similar incidence nephrotoxicity – Less several and moderate adverse effects – Less elimination time – Better neural tolerance – Less thromboembolic risk
Disadvantages	– - More moderate and several adverse effects – - Increase in blood volumen – - Decrease in hematocrit – Periferic arterial vasodilatation	– More light adverse reactions (0.58%)
Action on platelets	More activation and aggregation	Reduced activation and platelet aggregation

Figure 1: The properties of ionized and non-ionized contrast media.

The pathophysiological mechanisms that may result in platelet fall after exposure to contrast media are currently unknown; however, the mechanisms of thrombocytopenia induced by other drugs may be herein relevant:

1. Hapten-induced antibody: drug binds to platelet membrane and promotes antibody response.[22,23]
2. "Quinine-type antibody": drug binds to antibody Fab and/or membrane glycoprotein, thereby enhancing antibody affinity and binding to platelet glycoprotein.[24]
3. Autoantibody induction: drug induces formation of autoantibody that binds alone to platelet glycoprotein.[25]
4. Drug-specific antibody: antibody recognizes the monoclonal antibody bound to its target.[26]
5. Immune complexes: drug binds to platelet factor 4 inducing antibodies that activate platelets.[27]

6. Fibrinogen receptor antagonist-dependent antibody: drug binds to glycoprotein IIb/IIIa (GP IIb/IIIa) inducing conformational changes, then recognized by antibody.[28]

The diagnosis of contrast-induced thrombocytopenia is both underdiagnosed and challenging as the condition develops in patients with multiple comorbidities, usually involving other potential thrombocytopenia-inducing causes. The diagnostic criteria suggested by George (Figure 2) may be useful in this setting.

The suspected drug precedes thrombocytopenia and by its suspension, it is completely resolved.
The drug has been the only administrator before the onset of thrombocytopenia or has been followed with other drugs by the suspension of the same with a normal platelet count.
Other etiologies of thrombocytopenia are excluded.
Re-exposure to the drug produces thrombocytopenia.
According to these criteria, the diagnosis of thrombocytopenia of drug origin is classified as follows:
Definitive if all 4 criteria are met
Probable if criteria 1, 2 and 3 are met
Possible if only criterion 1 is met
Unlikely if none of the criteria is met.

Figure 2. George criteria for the diagnosis of drug-induced thrombocytopenia.

Diagnostic laboratory tests play a controversial role in the diagnosis of contrast-induced thrombocytopenia, as is also the case with other causes of drug-induced thrombocytopenia (other than heparin). According to the recommendations issued by the Scientific and Stardardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH),[29] in order to demonstrate a reaction to contrast accounting for thrombocytopenia the following must be met:

1. In vitro demonstration of a reaction following contrast administration.
2. Demonstration of binding to a specific immunoglobulin.
3. Platelets must represent the target for said binding.
4. At least two independent laboratories must demonstrate this reaction.

These criteria are massively difficult to meet, to the extent that only confirmation by one laboratory is required for less common drugs such as contrast [30], because of sample inconsistency, solubility, and concentration. Among laboratory tests flow cytometry and enzyme-linked immunosorbent assay (ELISA) are recommended, with positive results reflecting evidence of antibodies binding to platelets.

The treatment of contrast-induced thrombocytopenia is nonspecific. Standard measures for acute thrombocytopenia (platelet transfusion, plasma exchange, corticosteroids, infusion of specific immunoglobulins) may be used.

MATERIAL AND METHODS

This study was a comprehensive systematic review of all the evidence currently available about contrast-induced thrombocytopenia. The PRISMA-P guidelines systematic review protocol was adhered to.[31] A search of the literature was carried out in electronic databases such as Pubmed, Scopus, and Web of Sciencie (WoS) using the following search criterion: "contrast media-induced thrombocytopenia". All 18 cases reported in the literature were selected, and an analysis was undertaken of patient characteristics, clinical presentation form, concurrent presence of other potential triggers, treatment administered, and type of contrast medium involved. Bearing in mind the limitations entailed, an attempt was made at correlating platelet count fall profile and subsequent recovery for all patients.

RESULTS

The characteristics of patients in our review with a diagnosis of contrast-induced thrombocytopenia are listed in table 1.

Case	Age	Sex	Allergies	Contrast media	Baseline platelet counts	Nadir platelet counts	Time after ICM infusion	Treatment	Improvement time	Recovery time	Repeated
Wein 1982	29	M	No	Diatrizoate	250	4	1 day	Steroids	2 days	6 days	
Shojania 1985	57	F	NA	Diatrizoate	NA	21	1 day	No	NA	9 days	
Shojania 1985	60	M	NA	Diatrizoate	252	6	12 hours	PT	1 day	4 days	Yes
Lacy 1986	79	M	No	Diatrizoate	220	2	1 day	Diphenhydramine	9 days	12 days	Yes
Chang 1989	66	F	No	Diatrizoate	230	10	4 hours	PT	1 day	3 days	Yes
Kudoh 1991	52	M	No	Diatrizoate	233	8	2 hours	Steroids, PT	1 day	3 days	
Wiener 1995	66	F	No	Iopromide	310	1	8 hours	Steroids, Ig, PT	2 days	4 days	Yes
Ogasawara 1997	50	M	NA	Iopamidol	287	19	5 hours	PT	1 day	2 days	Yes
Ural 1998	NA	F	NA	Iopamidol	NA	8	24 hours	No	NA	20 days	
Saitoh 2001	70	M	NA	Iopamidol	NA	5	3 hours	Steroids, PT	1 day	1 day	
Bonnard 2004	74	M	NA	Iopamidol	223	3	1 hour	No	2 days	4 days	Yes
Bata 2012	72	M	NA	Ioversol	NA	2	40 minutes	Steroids, PT	1 day	5 days	
McCaulley 2013	22	F	Penicillin, codeine	Iopamidol	172	4	Immediate	Steroids	1 day	5 days	
Keach 2014	75	M	No	Iodixanol	260	<9	4 hours	No	2 days	5 days	Yes
Cubero 2017	47	M	NA	Ioxaglate	NA	0	6 hours	Steroids	NA	6 days	Yes
Ferreira 2017	71	F	No	NA	198	1	5 hours	No	4 days	8 days	
Park 2018	63	M	NA	Ioversol	109	2	6 hours	Steroids, PT	2 days	4 days	
Takeda 2020	43	F	NA	Iohexol	148	5	1 hour	No	4 hours	3 days	

Table 1: Cases reports published (M: male, F: female, NA: not available, IG: immunoglobulins, PT: platelets transfusion). Improvement time: platelet rising. Recovery time: platelets > 100 x 10^3. Repeated: recurrent event after administration of ICM.

In all cases patients experienced a fall in platelet count within the first 24 hours, and progressive return to normal from the second or third day until recovery was complete. This course is represented in figure 3 (of note, 2 cases are not included because of data unavailability).

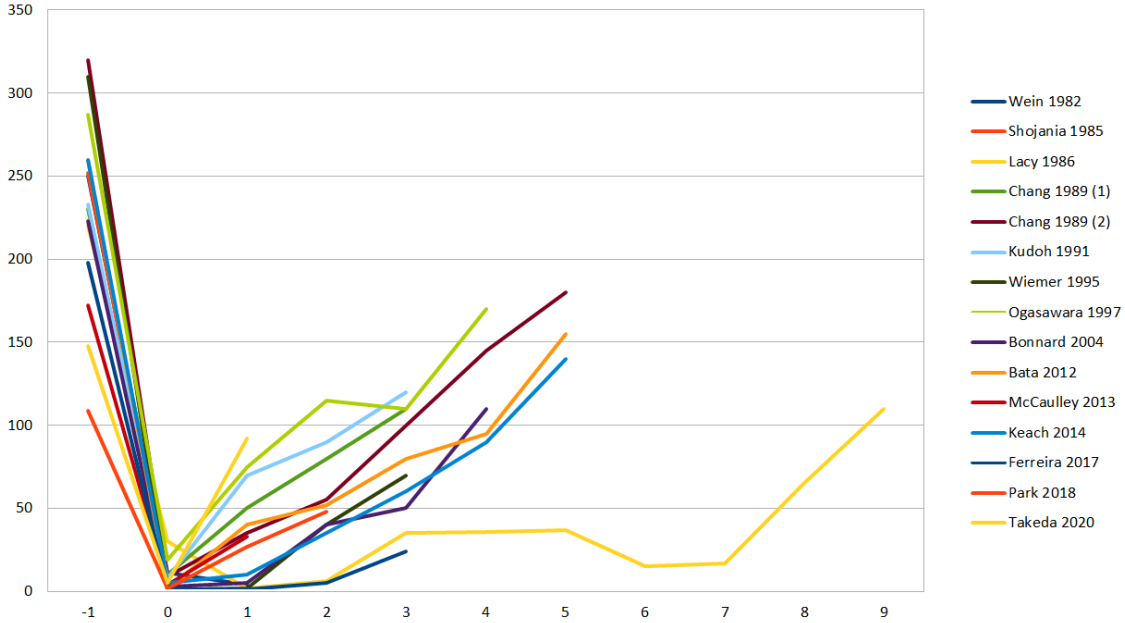

Figure 3: Evolution of platelet count in 14 case reports.

DISCUSSION

Contrast-induced thrombocytopenia is an extremely rare condition, hence available evidence relies on experience with a number of reported case series and their characteristics. Even in Hematology guidelines and manuals this adverse effect is overlooked because of its low incidence. Cases have been reported over the past 40 years and significant limitations exist in attempting to unveil shared features such as type of contrast medium and/or treatment choice. Most reported cases involve hyperosmolar iodinated contrast media (diatrizoate) in patients with a prior history of kidney failure, to the extent that presence of renal injury has been categorized as an additional risk factor. However, cases have also been reported involving hypoosmolar compounds similar to those currently used, showing a similar clinical profile and course of platelet count. All cases exhibit a normal platelet count at baseline, followed by an early, sudden decrease within 24 hours after exposure to the iodinated contrast (Figure 3). Platelet count had extreme falls to below 10 x 10^9/L (except for one case reported by Shojania et al,[5] whose nadir was 21x10^9/L), even to "0" in some cases, as in our patient.[16] Platelet count recovery starts within one day, with most patients reaching levels above 50 x 10^9/L at day three. This course may suggest a typical, acute lack of clinical-laboratory correlation, which (as discussed below) may account for the fact that severe thrombocytopenia bears in most cases no association with severe symptomatology in patients.

Among patients in our review who had iodinated contrast media-induced thrombocytopenia symptoms were highly diverse, encompassing cases ranging from asymptomatic[16] to (less often) with severe manifestations including significant bleeding, breathlessness, abdominal pain, hemodynamic variability, etc. We found no patient profile or comorbidity pattern allowing to predict severe symptomatology. Case reports by Takeda et al[18] and Cubero et al[16] are both potentially comparable as they refer to patients with similar comorbidities on hemodialysis. Despite this, presentation outcomes differed widely – the former case had moderate symptoms (gingival bleeding, desaturation) that required no specific treatment; recovery was complete at day three. In contrast, the case reported by Cubero et al. had no symptoms although treatment was initiated with steroids and recovery took some more time (at day 6). In view of all the above, at present we may safely say that contrast-induced thrombocytopenia is a scarcely predictable condition where also symptoms may develop or otherwise regardless of extent of platelet count reduction (no clinical-laboratory correlation).

The pathophysiological mechanism of decreased platelet count also remains unclear. In contrast with other types of drug-induced thrombocytopenia, the issue with contrast media raises more doubts, maybe because of the limited

number of available reports and scarce molecular understanding thereof, as no specific lab tests are available. In this regard, availability of diagnostic lab tests to elucidate what goes on early during presentation might provide additional information on the pathophysiological mechanisms involved, hence paving the way for future research. An immune-mediated mechanism has been posited following prior exposure to contrast[5], but cases are reported where no previous exposure occurred and thrombocytopenia developed, which renders this hypothesis seemingly irrelevant. Another mechanism that has been suggested is direct iodated contrast toxicity, but most specific lab tests yield negative results and, in some studies of patients with contrast-induced thrombocytopenia, bone marrow assessment reveals a normal number of megacariocytes.[7] Perhaps the most plausible theory is involvement of fibrinogen receptor antagonist-dependent antibodies, a mechanism that would result in conformational platelet changes by binding GPIIb/IIIa receptors, thus favoring the formation of platelet aggregates.[32] This mechanism would fit the platelet profile of patients in our review, namely sudden fall in platelet count (< 20 x 10^9/L), few symptoms, and faster recovery compared to other causes of thrombocytopenia. This mechanism might also account for complement cascade activation.[12,33,34]. However, as was mentioned above, the small yield of laboratory studies in this area results in high uncertainty in this respect, which should prompt further research.

The management of patients with contrast-induced thrombocytopenia is controversial. Of all cases studied, no treatment was used for 6, who only underwent observation and received support measures. In 8 cases steroid therapy was used, and 7 underwent platelet transfusions. This reflects a lack of general, evidence-based criteria, with individualized management being most appropriate as of today. Therefore, close clinical follow-up for the 2-3 days of severe fall in platelet count would perhaps be the best option, with stringent platelet count monitoring and treatment with steroids, plasmapheresis, immunoglobulins, and/or amines for complications such as bleeding, acute lung edema and/or anaphylaxis.

Finally, thrombocytopenia in association with non-iodinated contrast is anecdotal. A case of thrombocytopenia associated with gadolinium (*Gadoxetic acid disodium, Primovist, Bayer Healthcare, Germany*) has been recently reported in a patient with cirrhosis undergoing an abdominal MRI. This is an isolated case with no prior exposure, with previous comorbidity such as severe liver failure, where other potential causes were not ruled out, thus we shall not risk to acknowledge such association but rather wait for further similar case reports.[35]

CONCLUSIONS

Thrombocytopenia induced by iodinated contrast media is a rare, underdiagnosed complication following the administration of iodinated agents. Its mechanism remains unknown but an immune process is under consideration, which would induce a fall in platelet count within 24 hours after exposure to a contrast media. Recovery is also rapid, with no direct correlation between platelet count and presence of symptoms. Diagnostic laboratory tests are often unreliable for diagnosis since no precise pathogenic mechanism is currently known. Despite its exceptional status contrast-induced thrombocytopenia is a condition to be considered whenever a sudden, severe fall in platelet count occurs, followed by a similarly rapid recovery, after exposure to a iodinated contrast media.

Limitations in our study mainly derive from the reduced number of cases available, hence from inadequate experience regarding its diagnosis, management, and underlying pathophysiology. The series of cases we reviewed and updated are the only reports available, hence developing specific Units to make available appropriate laboratory tools for sample collection to units where iodinated contrast is used, such as interventional cardiology, radiodiagnosis, and/or other specialty units, would be of interest to gain an understanding of this condition. Similarly, a general registry for reporting suspected cases would be useful since the prevalence of the condition is likely underestimated.

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