

A prospective study of costs associated with the evaluation of allergic reactions to radiological contrast media

Running title: The costs of contrast allergy evaluation

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ABSTRACT

Background: The prevalence of hypersensitivity reactions to radiological contrast media (RCM) is increasing due to the greater performance of diagnostic and therapeutic tests that require RCMs.

Objective: We carried out a year-long real-life observational study to prospectively evaluate the patients referred to the Allergy Service from Primary Care, Emergency Room, and other Services with suspected moderate to severe RCM hypersensitivity.

Methods: To study the costs of RCM hypersensitivity evaluation, we systematically recorded direct and indirect costs.

Results: Sixty-nine patients with previous reactions to RCM were evaluated in the Allergy Service from June 1st, 2017, to May 31st, 2018. Total direct health care costs were € 10715.84, with a mean cost per patient of € 155.30 ± 77.08. Specifically, direct non-health costs reached € 1605.42 (mean € 23.27 ± 41.14), and indirect costs were € 6490.85 (mean € 94.07 ± 110.61). In summary, the total cost was € 18812.11, which means a mean cost of € 272.64 ± 164.77.

Conclusions: Our study reflects that the costs of an elective evaluation of hypersensitivity to RCM are low. This fact reaffirms that correct and safe management of these patients could be cost-effective, so our efforts should be directed to implement the necessary logistics.

Key words: Contrast media. Hypersensitivity. Health care costs. Diagnostic tests. Prospective studies.

RESUMEN

Antecedentes: La prevalencia de reacciones de hipersensibilidad a los medios de contraste radiológico (MCR) está aumentando debido al incremento en la realización de pruebas diagnósticas y terapéuticas que requieren MCR.

Objetivo: Hemos realizado un estudio observacional de un año de duración para evaluar prospectivamente a los pacientes remitidos al Servicio de Alergología con sospecha de reacciones moderadas a graves por hipersensibilidad a MCR.

Métodos: Para estudiar los costes de la evaluación de la hipersensibilidad a MCR, se registraron sistemáticamente los costes directos e indirectos.

Resultados: Se evaluaron 69 pacientes con reacciones previas a MCR remitidos al Servicio de Alergología desde el 1 de junio de 2017 hasta el 31 de mayo de 2018. Los costes sanitarios directos totales fueron 10715,84 €, con un coste medio por paciente de 155,30 € \pm 77,08. En concreto, los costes directos no sanitarios alcanzaron los 1.605,42 € (media 23,27 € \pm 41,14 €) y los costes indirectos fueron 6490,85 € (media 94,07 € \pm 110,61 €). En resumen, el coste total fue de 18812,11 €, lo que supone un coste medio de 272,64 \pm 164,77 €.

Conclusiones: Nuestro estudio refleja que los costes de una evaluación electiva de hipersensibilidad a MCR son bajos. Este hecho reafirma que el manejo correcto y seguro de estos pacientes podría ser rentable, por lo que nuestros esfuerzos deben estar dirigidos a implementar la logística necesaria.

Palabras clave: Medios de contraste. Hipersensibilidad. Costes sanitarios. Test diagnósticos. Estudios prospectivos.

INTRODUCTION

Within hypersensitivity reactions to radiological contrast media (RCM), the estimated prevalence of reactions to iodinated contrast media (ICM) is 1:170,000 patients (0.05-0.1%) [1]. Previous family and individual history of hypersensitivity reactions to ICM are considered risk factors, so presumably there is a possible genetic predisposition [2].

Regarding the clinical features, the cutaneous symptoms such as erythema and urticaria with or without angioedema are the most frequent (more than 70%) in immediate reactions. However, maculopapular eruptions are the most common expression of delayed reactions (30%-90%) [1], so skin symptoms are the most common presentation of reactions to ICMs [3]. Several studies have shown that non-immediate reactions with ICM are increasing, particularly with iodixanol [4, 5].

Skin tests and in vitro tests should be performed to diagnose both immediate and delayed reactions [1]. When reactions to ICMs have appeared in previous administrations, there are several factors to consider: the ICM involved and the severity of the reaction, the results of skin tests, the existence of cross-reactivity, and the availability of alternative ICMs [1]. Regarding which RCM to choose after a reaction has occurred, iobitridol has shown low cross-reactivity with other ICM and elicits fewer non-immediate reactions [6].

The classification of immediate reactions to radiological contrast media concerning severity includes: (i) mild reactions (itching, urticaria, nausea, mild vomiting); (ii) moderate reactions (severe vomiting, marked hives, asthma, facial edema, laryngeal edema, and vasovagal attack); and (iii) severe reactions (hypotension, shock, respiratory or cardiac arrest, and convulsion). Regarding delayed reactions, most of them are mild to moderate and self-limited, and most commonly associating maculopapular rashes, erythema, swelling, and pruritus [7].

The frequency of mild immediate reactions also depends on the type of RCM administered: ionic (3.8-12.7%) or non-ionic (0.7-3.1%) [8]. Severe immediate reactions to ionic RCM occur at 0.1-0.4

% of patients and fatal reactions occur in 1-3/100,000 RCM injections [8]. Because of this, non-ionic RCMs should be used.

The elective evaluation of alleged reactions to RCMs allows the unlabeled of patients not allergic to these compounds and permits the selection of an RCM to be administered in future explorations in patients diagnosed as allergic [1, 2].

Nevertheless, this evaluation is not without costs. As far as we know, no prospective studies have addressed the cost of RCM hypersensitivity evaluation. Even more, few prospective studies about the costs of elective evaluation of drug allergy are available and have been performed with other drugs such as beta-lactams [9-11] and nonsteroidal anti-inflammatory drugs (NSAID) [12]. A complete evaluation could reduce the risk of possible reactions when patients are re-exposed to RCM in the future. This aspect is crucial to assess whether the allergy study can be cost-effective. Therefore, the importance of the evaluation of hypersensitivity to RCM lies not only in the cost, but also in the usefulness of the tests results.

Our objective was to evaluate the costs associated with the elective study of patients with suspected hypersensitivity to RCMs prospectively.

METHODS

A one-year real-life prospective observational study was designed to evaluate the costs associated with the work up diagnosis of all patients who consulted the Allergy Service for suspected previous reactions with RCMs. The study lasted from June 1st, 2017, to May 31st, 2018, and its protocol was reviewed and approved by the hospital's Ethics Committee (PI4505/2017). Other parts of the entire study, related to hypersensitivity to beta-lactams or NSAIDs, have been previously published [10-12].

All patients who attended the Allergy Service during the study period due to suspected hypersensitivity reactions to RCMs were proposed to be included. They were referred to the Allergy Service from Primary Care (25 of 69 patients, 36.23 %), Emergency Room (6 patients, 8.70 %), and other Hospital Services (38 patients, 55.07 %) because of moderate to severe reactions to one or more RCMs and a high probability of needing them in the future.

Patients whose reactions occurred within the first hour after RCM administration, with clinical symptoms such as urticaria and/or angioedema, anaphylaxis, or bronchospasm, were included. Those patients with late reactions occurring after the first hour of RCM administration (maculopapular rash and other severe skin reactions) were also included. Although late reactions are generally mild skin reactions, the risk of more severe skin reactions when re-exposed led us to include these patients in the study. All patients who voluntarily agreed to be included in the study signed a written informed consent form.

Methodology of the RCM hypersensitivity evaluation

For diagnostic procedures, international guidelines (European Network for Drug Allergy / European Academy of Allergy and Clinical Immunology) to evaluate hypersensitivity reactions to RCM were followed [13]. When immediate reactions occurred, after a complete clinical history, the patients underwent skin prick and intradermal tests with immediate reading. For delayed reactions, intradermal tests were performed with readings at 24 and 48 hours and patch tests with RCMs when the attending allergist considered necessary.

A standard set of reagents was used (Tables 1 and 2; supplementary material). If skin test results were negative, patients underwent a single-blind, placebo-controlled intravenous challenge test with the suspected RCM up to the standard dose. The algorithms proposed for diagnosing immediate and delayed reactions by Sánchez-Borges et al. [14] have been followed.

All visits were prospectively recorded. The medical history was obtained on the first visit, but skin tests and RCM challenge tests, when performed, were carried out at subsequent visits. When positive results appeared, more visits were required to verify tolerance to at least one alternative RCM.

For data collection, a structured questionnaire was completed for each patient. (Table 3; supplementary material). Furthermore, to maintain anonymity, the data obtained was stored in a dissociated database.

Assessment of costs

The Bureau of Management of the hospital provided personnel, material, and infrastructure costs at our hospital. Data on the study's medication were collected in a structured way; data related to the costs of such medication were supplied by the Hospital Pharmacy Service (Table 4; supplementary material).

The data in monetary terms taken into account to evaluate the costs were:

- Reagents and RCM for skin and challenge tests.
- Health and administrative staff fees.
- Building maintenance expenses.
- Travel costs.
- Absenteeism of patients.

a) Direct health costs

The number of visits, all diagnostic tests performed (skin, patch and challenge tests), and costs associated with personnel and materials were considered to assess the direct health costs. Data on materials and infrastructures are detailed in Table 5, supplementary material.

The total amounts attributable to the Allergy Service were divided by the total visits to the Allergy Service of all patients evaluated for any reason throughout 2017 to calculate the cost per visit related

to staff fees (payroll and insurance) and building maintenance costs (water, electricity, and others). In the Spanish National Health Service, the remuneration of the staff does not depend on medical acts, so we have assumed that the cost of each visit for this concept was the same (Table 6; supplementary material). The Hospital Management provided this datum.

Subsequently, the costs for these concepts attributable to the study patients were calculated, taking into account the cost per visit and the number of visits for each patient. Depreciation costs for the building use were not considered.

b) Direct non-health costs

The direct non-health cost was calculated for each patient based on of the number of visits and the distance (km) from their home to hospital. Almost all the patients resided in the province of Salamanca (331,000 inhabitants). It was considered that patients residing outside the city of Salamanca came by car. A travel expense of € 0.19 per kilometer was assumed because it is the amount that the Spanish authorities pay to public officials [15]. Patients residing in the small city of Salamanca (144,000 inhabitants) were supposed to arrive on foot.

c) Indirect costs

To estimate indirect costs, the loss of working hours (absenteeism) was considered. For patients employed by third parties, the amount was obtained based on the average labor cost per hour in 2018 in the European Union (EU), estimated at € 27.4 [16]. In order to give some value to the hours dedicated to allergic evaluation by unemployed patients, the mean \pm standard deviation (SD) of the basic minimum hourly wage in the EU (4.38 ± 3.01 €) was considered [17].

Statistical analysis

We analyzed all the data using IBM® SPSS Statistics V25.0 (Armonk-IBM Corp., New York, USA).

A statistically significant result was considered when $p < 0.05$. For the description of the variables,

the mean and SD were used for quantitative variables and the relative frequencies for qualitative ones. For comparing quantitative variables, non-parametric (Mann-Whitney test) and parametric (T-test for independent samples) tests were performed.

RESULTS

Sixty-nine patients with suspected hypersensitivity to RCM were evaluated in our Allergy Service from June 1st, 2017, to May 31st, 2018. Sixty-six completed the study (95.7 %). Mean age was 57.8 ± 16.8 years, and women were 56.5 %. The reactions that led to a referral to the Allergy Service were immediate in 29 patients (42.0 %) and delayed in 40 (58.0 %).

Regarding patients with immediate reactions, 21 of 29 patients (72.41 %) had moderate reactions associating urticaria (14 patients: 66.67 %), bronchospasm (4 patients: 19.05 %) and severe vomiting (3 patients: 14.29 %). Moreover, 8 of 29 patients (27.59 %) had severe reactions associating with life-threatening anaphylaxis. On the other hand, patients with delayed reactions (40 patients) had all maculopapular rash reactions.

Hypersensitivity to RCMs was demonstrated in 15 patients (21.7 %) who had previously suffered a total of 20 reactions. Of the 15 patients with a final diagnosis of hypersensitivity to RCM, twelve of them had presented skin reactions (eleven delayed reactions and one immediate reaction), whereas three patients had anaphylaxis. Regarding the index reaction, four of these 15 patients had presented immediate reactions (26.7 %) and eleven delayed ones (73.3 %) (Table 1). Eleven patients were diagnosed by skin tests (73.3 %), whereas the remaining four required challenge tests (26.7 %). In twelve of them, tolerance to an alternative RCM was proved (Table 2).

A mean of 4.22 ± 1.48 (SD) visits was required to complete the diagnosis, and no statistically significant difference was found between patients in whom hypersensitivity to RCM was confirmed (4.73 ± 1.34) and those in whom it was discarded (4.07 ± 1.52) (Mann Whitney p-value = 0.098).

However, the mean number of visits between patients with had presented immediate (3.34 ± 1.23) and delayed (4.85 ± 1.35) reactions was significantly different (p -value < 0.001).

The median (interquartile range: IQR) of the hours spent in each visit was four hours (Q1: three hours and thirty minutes, Q3: four hours). There is a significant difference ($p = 0.001$) between patients diagnosed of hypersensitivity to RCM (four hours and twenty minutes) and patients with hypersensitivity ruled out (three hours and forty-seven minutes). On the other hand, there is no significant difference ($p = 0.346$) between patients who had immediate reactions (three hours and forty-five minutes) and those with delayed reaction (four hours).

Direct health costs

The total costs of personnel and materials were € 8,087.02. Of these, € 261.50 corresponded to the cost of materials and infrastructure, and € 7,825.52 to healthcare personnel expenses (including the payroll and insurance of the Allergy Service Personnel: doctors, nurses, assistants, and administrative staff) (Tables 5 and 6; supplementary material). The costs of performing the skin tests ($n=68$) and the patch tests ($n=20$) reached € 121.11. This cost includes only consumable material (lancets, syringes, gloves...). The cost of the RCM provocation tests (60 patients), including the cost of the RCM used, amounted to € 2,507.71. Here it is included the costs of drugs employed for drug challenge tests and skin tests. We include it in this section (challenge tests) because the main use of these drugs is for provocation tests and, residual, for skin tests. Finally, the total direct health care costs were up to € 10,715.84, with a mean cost per patient of € 155.30 ± 77.08 (Table 3).

Direct non-health costs

Of the 69 studied patients, 28 came from places out of the city, and, as aforementioned, we assumed that they came by car. The total mean distance traveled was 301.77 ± 248.94 km, representing an

average cost of € 57.34 ± 47.30. Direct non-health costs reached € 1,605.42 (Table 3). The data relating to travel expenses showed an asymmetrical distribution due to some outliers, with a mean of € 23.27 ± 41.14.

Indirect health costs

In Spain, when employees go to a medical consultation, they do not have any salary reduction, so the cost is mainly reflected in the loss of income for the employer. Therefore, indirect healthcare costs were calculated based on patient absenteeism (26 of 69 patients; 37.7%). Regarding the rest of the patients (unemployed, retired), we assume that the loss of their housework should be considered equivalent to the minimum hourly wage. Thus, the total indirect costs reached € 6,490.85 (Table 3), and the mean loss of income was € 94.07 ± 110.61.

Total costs

In summary, the total cost of the allergologic evaluation reached € 18,812.11, with a minimum per patient of € 66.41, a maximum of € 752.45, and an average cost of € 272.64 ± 164.77 (Table 3). When we compare patients whose hypersensitivity to RCM was confirmed with those who did not, mean costs were € 355.85 ± 207.10 and € 249.52 ± 144.91 respectively, being a statistically significant difference ($p = 0.047$). The mean cost of patients with immediate (€ 228.07 ± 171.35) and delayed (€ 303.58 ± 158.87) reactions was also statistically significantly different ($p = 0.008$).

As expected, total expenses were significantly higher in patients who worked for pay (€ 369.54 ± 186.76) than in unemployed patients (€ 214.05 ± 117.76) (p -value<0.001).

DISCUSSION

In recent years, diagnostic and therapeutic tests requiring RCMs, mainly computerized tomography, and magnetic resonance imaging, have been notably increased [1]. Thus, more than 75 million tests per year are performed worldwide with RCM, and this has led to an increase in the prevalence of adverse reactions, including hypersensitivity reactions, mainly to ICMs [1]. Therefore, it is essential to correctly diagnose all these patients and offer them safe alternatives, as they can need RCMs throughout their lives.

To our knowledge, no prospective study has been published focusing on the cost evaluation of elective allergy testing in patients who previously had possible reactions to RCMs. That is an important issue since the correct diagnosis of these patients will influence the avoidance of new reactions, which would increase healthcare resources and costs.

Even if we consider similar diagnostic procedures (as might be the case for drug hypersensitivity), only four prospective studies have addressed elective drug allergy evaluation costs, three performed in adults and one in children. Thus, Blumenthal et al. [9] performed a prospective estimation of the cost of penicillin allergy evaluation in 30 adult outpatients. In this study, the authors consider the basic case when oral provocation tests were performed without previous skin tests reaching a cost of \$ 220 (€ 209.37). This amount could be as high as \$ 540 (€ 482.45) for patients undergoing skin tests, due to the increased number of visits required. Moreover, Sobrino-García et al. [10, 11] performed a prospective study of 296 adults and 40 children who attended for suspected beta-lactams allergy, obtaining a mean cost of € 187.49 ± 148.14 and € 275.27 ± 164.70 per patient, respectively. In a prospective study evaluating the cost of elective NSAID hypersensitivity studies, the mean cost reached € 185.30 ± 146.77 [12].

This prospective, one-year study evaluated all direct and indirect health costs in 69 patients with suspected hypersensitivity reactions to RCM. The mean cost per patient reached € 272.64 ± 164.77.

Of this figure, direct health costs were € 155.30 ± 77.08, direct non-health costs € 23.27 ± 41.14, and indirect health costs € 94.07 ± 110.61 (Table 3). The mean number of visits required to complete the diagnosis was 4.22. Direct and indirect healthcare costs are the principal part of the costs.

Regarding direct healthcare costs, the number of visits is the basis of the amount reached in each patient. On the other hand, indirect health costs are mainly due to the loss of patient wages and the cost of the minimum hourly wage, and the number of visits. Thus, the number of visits required is decisive to explain the differences between hypersensitivity vs. non-hypersensitivity reactions, immediate vs. non-immediate reactions, and employed vs. non-employed patients. In turn, the number of visits is determined by the protocol used to evaluate the hypersensitivity to RCM.

If we compare the total costs of our study with those of the studies of hypersensitivity to drugs (such as beta-lactams and NSAIDs) carried out in the same context, we can see that they are higher than these: € 272.64 (RCM) vs. € 187.49 (beta-lactams) [10] and € 185.30 (NSAIDs) [12]. That is probably because, in the case of de-labeling of hypersensitivity to RCM, the higher proportion of non-immediate reactions and patch tests performed entails a more significant number of visits. In addition, in terms of direct health costs, the costs of provocation tests are higher than those of hypersensitivity to drugs, [10, 12] the opposite than skin tests [10].

Finally, our study has some limitations. We have made the estimates taking into account the total number of patients and not the medical acts performed. In Spain, the payment to the employees of the National Health Service is not determined by the medical acts performed. Furthermore, when evaluating the resulting amounts, it should be considered that gross earnings from work are different between EU countries. Spain ranks 13th in the ranking of the 28 EU countries, both in hourly labor costs and in gross average hourly wages [16]. That is why we must bear in mind that indirect costs will be different in other countries. Besides, direct costs could also be different among EU countries. Therefore, the main limitation is that these figures are valid only for costs in the country where this

study was carried out (Spain). However, the study can serve as an approximation for other countries and give a global idea of the costs.

To sum up, in this prospective study, in which direct and indirect healthcare costs of the RCM hypersensitivity study were systematically evaluated in an outpatient clinic, a complete elective study of suspected RCM hypersensitivity reached € 272.64 ± 164.77 per patient. Therefore, our study reflects that the costs of an elective evaluation of hypersensitivity to RCM are low, even more considering all the costs of imaging procedures. This fact reaffirms that correct and safe management of these patients could be cost-effective, so efforts should be directed to implement the necessary allergic studies, particularly considering that hypersensitivity reactions to RCMs are increasing.

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FINANCIAL SOURCE STATEMENT

The authors declare that they have no financial sources.

CONFLICTS OF INTERESTS

The authors have no conflicts of interests to declare.

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Table 1. Pre-study clinical manifestations and RCM implicated in patients finally diagnosed with hypersensitivity to RCM.

		Skin reactions		Anaphylaxis
		Immediate	Non-immediate	
Iodinated contrast media	Iobitridol	-	1	1
	Iodixanol	-	7	-
	Iohexol	1	4	-
	Ioversol	-	3	1
	Iopromide	-	1	
Non-iodinated contrast media	Gadobutrol	-	-	1
TOTAL		1	16 ^(a)	3

(a) One patient had delayed reactions with two different contrast media, and two patients had delayed reactions with three different contrast media. Therefore, the 16 delayed reactions occurred in a total of 11 patients.

Table 2. Positive tests results in patients finally diagnosed with hypersensitivity to RCM.

PATIENT #	Positive skin tests			Positive challenge tests	Challenge test with alternative RCM
	Prick tests +	ID tests +	Patch tests +		
1	-	-	-	iobitridol	iodixanol
2	-	iohexol	iodixanol iohexol	ND	iobitridol
3	-	-	ND	iohexol	iobitridol
4	-	iodixanol	ND	ND	iobitridol
5	-	iodixanol	ND	ND	iobitridol
6	-	iodixanol iohexol ioversol	iodixanol	ND	ND
7	-	iodixanol	-	ND	iobitridol
8	-	-	ND	iopromida	ND
9	-	-	-	iobitridol	ND
10	-	ioversol	ND	ND	iohexol ^(a)
11	-	iodixanol iohexol ioversol	-	ND	iobitridol
12	-	iohexol ioversol	ND	ND	iobitridol
13	-	iodixanol iohexol ioversol	iodixanol ioversol	ND	iobitridol
14	-	iodixanol	ND	ND	iobitridol
15	-	gadobutrol	ND	ND	sodium gadoxetate

RCM: radiologic contrast media; ID: intradermal; ND: not done.

(a) The challenge test with an alternative RCM was also positive.

Table 3. Total costs and percentages differentiated by items and types of costs.

Item	n	Cost (%)	Type of Cost	Total cost (%)	Mean cost (SD)
Skin and patch tests	68	€ 121.11 (0.64)	Direct health costs	€ 10,715.84 (56.96)	€ 155.30 (77.08)
Challenge tests	60	€ 2,507.71 (13.33)			
Materials and infrastructure	69	€ 261.50 (1.39)			
Health personnel fees	69	€ 7,825.52 (41.60)			
Travel expenses	69	€ 1,605.42 (8.53)	Direct non-health costs	€ 1,605.42 (8.53)	€ 23.27 (41.14)
Loss of working days	69	€ 6,490.85 (34.50)	Indirect health costs	€ 6,490.85 (34.50)	€ 94.07 (110.61)
TOTAL				€ 18,812.11 (100)	€ 272.64 (164.77)