

A Prospective Study of Costs Associated With the Evaluation of Allergic Reactions to Radiological Contrast Media

Sobrinó-García M^{1,2}, Muñoz-Bellido FJ^{1,2,3}, Moreno E^{1,2,3,4}, Gracia-Bara MT^{1,2}, Laffond E^{1,2,3}, Lázaro-Sastre M¹, Martín-García C^{1,2}, Dávila I^{1,2,3,4}

¹Allergy Department, University Hospital of Salamanca, Spain

²Institute for Biomedical Research of Salamanca, IBSAL, Salamanca, Spain

³Department of Biomedical and Diagnostic Sciences, Faculty of Medicine, University of Salamanca, Spain

⁴Asthma, Allergic and Adverse Reactions (ARADyAL) Network for Cooperative Research in Health of Instituto de Salud Carlos III, Salamanca University Hospital, Salamanca, Spain

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■ Abstract

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

Objective: We carried out a year-long real-life observational study to prospectively evaluate patients referred to the allergy department from primary care, the emergency department, and other specialties with suspected moderate-to-severe RCM hypersensitivity reactions.

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

Results: Sixty-nine patients with previous reactions to RCM were evaluated in the allergy department from June 1, 2017, to May 31, 2018. Total direct health care costs were €10 715.84, with a mean (SD) cost per patient of €155.30 (77.08). Specifically, direct non-health care 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 €18 812.11, that is, a mean cost of €272.64 (164.77).

Conclusions: Our study shows that the costs of an elective evaluation of hypersensitivity reactions to RCM are low, thus confirming that correct and safe management of affected patients are cost-effective. Therefore, our efforts should be directed toward ensuring 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 de 10.715,84 €, con un coste medio por paciente de 155,30 € ± 77,08. En concreto, los costes directos no sanitarios alcanzaron los 1.605,42 € (media 23,27 € ± 41,14 €) y los costes indirectos fueron de 6.490,85 € (media 94,07 € ± 110,61 €). En resumen, el coste total fue de 18.812,11 €, lo que supone un coste medio de 272,64 ± 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]. Given that a previous family history and an individual history of hypersensitivity reactions to ICM are considered risk factors, genetic predisposition seems likely [2].

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

Both immediate and delayed reactions should be diagnosed based on skin and *in vitro* tests [1]. When reactions to ICMs have appeared in previous administrations, it is important to consider the ICM involved, the severity of the reaction, the results of skin tests, the presence of cross-reactivity, and the availability of alternative ICMs [1]. When selecting an RCM after a reaction has occurred, it is important to remember that iobitridol has shown low cross-reactivity with other ICM and elicits fewer nonimmediate reactions [6].

Immediate reactions to RCM are classified by severity as follows: (i) mild reactions (itching, urticaria, nausea, and mild vomiting); (ii) moderate reactions (severe vomiting, marked hives, asthma, facial edema, laryngeal edema, and vasovagal syncope); and (iii) severe reactions (hypotension, shock, respiratory or cardiac arrest, and convulsion). Delayed reactions are mainly mild-to-moderate and self-limiting and most commonly involve maculopapular rash, erythema, swelling, and pruritus [7].

The frequency of mild immediate reactions also depends on the type of RCM administered, with ionic RCM responsible for 3.8%-12.7% and nonionic RCM responsible for 0.7%-3.1% [8]. Severe immediate reactions to ionic RCM affect 0.1%-0.4 % of patients, and fatal reactions occur in 1-3 per 100 000 RCM injections [8]. Therefore, nonionic RCMs are preferred.

The elective evaluation of alleged reactions to RCMs makes it possible to delabel patients who are not allergic to these compounds and select an RCM to be administered in future examinations in allergic patients [1,2].

Nevertheless, this evaluation is not without costs. As far as we know, no prospective studies have addressed the cost of evaluating hypersensitivity reactions to RCM. Moreover, few prospective studies have assessed the costs of elective evaluation of drug allergy, and those that have were based on other drugs such as β -lactams [9-11] and nonsteroidal anti-inflammatory drugs (NSAIDs) [12]. A complete evaluation could reduce the risk of reactions when patients are re-exposed to RCM in the future. This aspect is crucial when assessing whether the allergy study is cost-effective. Therefore, the importance of evaluating hypersensitivity to RCM lies not only in the cost, but also in the usefulness of the test results.

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

Methods

A 1-year, real-life prospective observational study was performed to evaluate the costs associated with the diagnostic work-up of all patients who consulted the allergy department for suspected previous reactions to RCMs. The study lasted from June 1, 2017, to May 31, 2018, and the protocol was reviewed and approved by the local ethics committee (PI4505/2017). Our group has previously reported data on hypersensitivity to β -lactams and NSAIDs [10-12].

The study population comprised patients who attended the allergy department during the study period with suspected hypersensitivity reactions to RCMs. Patients were referred to the allergy department from primary care (25 of 69 patients, 36.23%), the emergency department (6 patients, 8.70%), and other specialties (38 patients, 55.07%) because of moderate-to-severe reactions to 1 or more RCM and a high probability of needing RCM in the future.

Patients whose reactions occurred within the first hour after administration of the RCM and who developed clinical symptoms such as urticaria and/or angioedema, anaphylaxis, and bronchospasm, were included; patients with late reactions occurring after the first hour of administration (maculopapular rash and other severe skin reactions) were also included. Although late reactions generally take the form of 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

International guidelines (European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology) on evaluation of hypersensitivity reactions to RCM were followed during the diagnostic work-up [13]. When immediate reactions occurred, a complete clinical history was taken, and the patients underwent skin prick and intradermal tests with an 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 them 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. We followed the algorithms proposed by Sánchez-Borges et al [14] for diagnosing immediate and delayed reactions.

All visits were prospectively recorded. The medical history was obtained at the first visit, although the 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 1 alternative RCM.

Each patient completed a structured questionnaire (Table 3; Supplementary material). Furthermore, to maintain anonymity, data were stored in a dissociated database.

Assessment of Costs

The personnel, material, and infrastructure costs at our hospital were covered by the Management Bureau. Data on the study medication were collected in a structured fashion; data on medication costs were provided by the hospital pharmacy (Table 4; Supplementary material).

Costs were evaluated based on the following:

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

Direct health care costs

The number of visits, all diagnostic tests performed (skin, patch, and challenge tests), and costs associated with personnel and materials were recorded 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 department were divided by the total visits to the department by all patients evaluated for any reason during 2017 to calculate the cost per visit related to staff fees (payroll and insurance) and building maintenance (water, electricity, and other). In the Spanish National Health Service, staff remuneration does not depend on medical acts; therefore, we assumed that the cost of each visit for this concept was the same (Table 6; Supplementary material). This information was provided by the Management Bureau.

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 per patient. Building depreciation costs were not considered.

Direct non-health care costs

The direct non-health care cost was calculated based on of the number of visits and the distance (km) from the patient's home to the hospital. Almost all the patients resided in the

province of Salamanca (331 000 inhabitants). Patients residing outside the city of Salamanca were considered to have come by car. A travel expense of €0.19 per kilometer was assumed based on the amount that the Spanish authorities pay to public officials [15]. Patients residing in the small city of Salamanca (144 000 inhabitants) were considered to arrive on foot.

Indirect costs

Indirect costs were estimated based on the loss of working hours (absenteeism). 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), which has been estimated at €27.40 [16]. In order to give some value to the hours dedicated to evaluation of allergy by unemployed patients, the mean (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, Version 25.0 (IBM Corp.). Statistical significance was set at $P < .05$. Quantitative variables are expressed as mean (SD) and qualitative variables as relative frequencies. Quantitative variables were compared using the Mann-Whitney test and the t test for independent samples.

Results

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

Regarding patients with immediate reactions, 21 (72.41%) had moderate reactions with urticaria (14 patients [66.67%]), bronchospasm (4 patients [19.05%]), and severe vomiting (3 patients [14.29%]). Moreover, 8 patients (27.59%) experienced life-threatening anaphylaxis. All patients with delayed reactions (40 patients) developed maculopapular rash.

Hypersensitivity to RCMs was demonstrated in 15 patients (21.7%) who had previously experienced a total of 20 reactions.

Table 1. Pre-study Clinical Manifestations and RCM Implicated in Patients Eventually Diagnosed With Hypersensitivity to RCM

		Skin reactions		Anaphylaxis
		Immediate	Nonimmediate	
Iodinated contrast media	Iobitridol	-	1	1
	Iodixanol	-	7	-
	Iohexol	1	4	-
	Ioversol	-	3	1
	Iopromide	-	1	-
Noniodinated contrast media	Gadobutrol	-	-	1
	Total	1	16 ^a	3

Abbreviation: RCM, radiologic contrast media.

^aOne patient had delayed reactions with 2 different contrast media, and 2 patients had delayed reactions with 3 different contrast media. Therefore, the 16 delayed reactions occurred in a total of 11 patients.

Table 2. Positive Tests Results in Patients Eventually 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	-	Io hexol	Iodixanol Io hexol	ND	Iobitridol
3	-	-	ND	Io hexol	Iobitridol
4	-	Iodixanol	ND	ND	Iobitridol
5	-	Iodixanol	ND	ND	Iobitridol
6	-	Iodixanol Io hexol Ioversol	Iodixanol	ND	ND
7	-	Iodixanol	-	ND	Iobitridol
8	-	-	ND	Iopromida	ND
9	-	-	-	Iobitridol	ND
10	-	Ioversol	ND	ND	Io hexola
11	-	Iodixanol Io hexol Ioversol	-	ND	Iobitridol
12	-	Io hexol Ioversol	ND	ND	Iobitridol
13	-	Iodixanol Io hexol Ioversol Ioversol	Iodixanol ND	Iobitridol	
14	-	Iodixanol	ND	ND	Iobitridol
15	-	Gadobutrol	ND	ND	Sodium gadoxetate

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

^aThe challenge test with an alternative RCM was also positive.

Of the 15 patients eventually diagnosed with hypersensitivity to RCM, 12 had experienced skin reactions (11 delayed reactions and 1 immediate reaction), whereas 3 experienced anaphylaxis. Regarding the index reaction, 4 of these 15 patients had immediate reactions (26.7%) and 11 delayed reactions (73.3%) (Table 1). Eleven patients were diagnosed based on skin tests (73.3%), whereas the remaining 4 required challenge tests (26.7%). In 12 cases, tolerance to an alternative RCM was proved (Table 2).

A mean of 4.22 (1.48) 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 ruled out (4.07 [1.52]) ($P=0.098$). However, the difference in the mean number of visits between patients who had an immediate reaction (3.34 [1.23]) and those who had a delayed reaction (4.85 [1.35]) was significant ($P<0.001$).

The median (IQR) time spent at each visit was 4 hours (3 hours, 30 minutes to 4 hours). There was a significant difference ($P=0.001$) between patients diagnosed with hypersensitivity to RCM (4 hours and 20 minutes) and patients in whom hypersensitivity was ruled out (3 hours and 47 minutes). On the other hand, there was no significant

difference ($P=0.346$) between patients who had immediate reactions (3 hours and 45 minutes) and those who had delayed reactions (4 hours).

Direct Health Care Costs

Total personnel and material costs amounted to €8087.02. Of these, €261.50 corresponded to the cost of materials and infrastructure, and €7825.52 to health care personnel expenses (including the payroll and insurance of allergy department staff, ie, doctors, nurses, assistants, and administrative staff) (Tables 5 and 6, Supplementary material). The cost of performing the skin tests ($n=68$) and the patch tests ($n=20$) reached €121.11. This cost includes only consumable material (eg, lancets, syringes, gloves). The cost of the RCM challenge tests (60 patients), including the cost of the RCM used, amounted to €2507.71. This figure includes the costs of drugs used for drug challenge tests and skin tests. We include it in this section (challenge testing) because the main use of these drugs is for challenge tests and, occasionally, for skin tests. Finally, the total direct health care costs reached €10 715.84, with a mean cost per patient of €155.30 (77.08) (Table 3).

Table 3. Total Costs and Percentages Differentiated by Items and Types of Costs

Item	No.	Cost, %	Type of cost	Total cost, %	Mean (SD) cost
Skin and patch tests	68	€121.11 (0.64)	Direct health care costs	€10 715.84 (56.96)	€155.30 (77.08)
Challenge tests	60	€2507.71 (13.33)			
Materials and infrastructure	69	€261.50 (1.39)			
Health care personnel fees	69	€7825.52 (41.60)	Direct non-health care costs	€1605.42 (8.53)	€23.27 (41.14)
Travel expenses	69	€1605.42 (8.53)			
Loss of working days	69	€6490.85 (34.50)	Indirect health care costs	€6490.85 (34.50)	€94.07 (110.61)
Total				€18 812.11 (100)	€272.64 (164.77)

Direct Non-Health Care Costs

Of the 69 patients studied, 28 were from outside the city of Salamanca, and, as mentioned above, 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 care costs reached €1605.42 (Table 3). The data relating to travel expenses showed an asymmetrical distribution resulting from outliers, with a mean of €23.27 (41.14).

Indirect Health Care Costs

In Spain, when employees visit their doctor, their salary is not reduced; the cost is reflected in the loss of income for the employer. Therefore, indirect health care costs were calculated based on patient absenteeism (26 of 69 patients [37.7%]). Regarding the remaining patients (unemployed, retired), we assumed that the loss of their housework should be considered equivalent to the minimum hourly wage. Thus, the total indirect costs reached €6490.85 (Table 3), and the mean loss of income was €94.07 (110.61).

Total Costs

In summary, the total cost of the allergology work-up 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 compared patients in whom hypersensitivity to RCM was confirmed with those in whom it was not, mean costs were €355.85 (207.10) and €249.52 (144.91), respectively, the difference being statistically significant ($P=0.047$). The difference in mean cost between patients with immediate reactions (€228.07 [171.35]) and those with delayed reactions (€303.58 [158.87]) was also statistically significant ($P=0.008$).

As expected, total expenses were significantly higher in salaried patients (€369.54 [186.76]) than in unemployed patients (€214.05 [117.76]) ($P<0.001$).

Discussion

The use of medical investigations, mainly computed tomography and magnetic resonance imaging, has become

increasingly frequent for diagnosis and treatment of RCM [1]. More than 75 million tests per year are performed worldwide to assess RCM, thus leading to an increase in the prevalence of adverse reactions, including hypersensitivity reactions, mainly to ICMs [1]. Therefore, it is essential to correctly diagnose affected patients and offer them safe alternatives, since they may need RCMs throughout their lives.

To our knowledge, no prospective study has evaluated the cost of elective allergy testing in patients suspected of having experienced reactions to RCMs. This area is worthy of serious investigation, since appropriate diagnosis could prevent new reactions, which would increase the use of health care resources and associated costs.

Taking into consideration similar diagnostic procedures (eg, drug hypersensitivity), only 4 prospective studies have addressed elective evaluation of drug allergy costs (3 in adults and 1 in children). Thus, Blumenthal et al [9] prospectively estimated the cost of evaluating penicillin allergy in 30 adult outpatients and found that oral challenge tests, even without previous skin tests, cost \$220 (€209.37). This amount could be as high as \$540 (€482.45) for patients undergoing skin tests, owing 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 β -lactam 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 assessment, the mean cost reached €185.30 (146.77) [12].

This prospective, 1-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 nonhealth 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 health care comprises the main part of the costs.

Regarding direct health care 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, the cost of the minimum hourly wage, and the number of visits. Thus, the number of visits required is decisive when accounting for differences between hypersensitivity and nonhypersensitivity reactions, immediate and nonimmediate reactions, and employed and nonemployed patients. In turn, the number of visits is determined by the protocol used to evaluate hypersensitivity to RCM.

If we compare the total costs of our study with those of studies of hypersensitivity to drugs (eg, β -lactams and NSAIDs) carried out in the same context, we can see that they are higher (€272.64 [RCM] vs €187.49 [β -lactams] [10] and €185.30 [NSAIDs] [12]), probably because, in the case of delabeling of hypersensitivity to RCM, the greater number of nonimmediate reactions and patch tests performed entails a more significant number of visits. In addition, in terms of direct health costs, the costs of challenge tests are higher than those of hypersensitivity to drugs [10,12], in contrast with skin tests [10].

Our study is subject to a series of limitations. We made the estimates taking into account the total number of patients and not the medical acts performed. In Spain, remuneration of National Health Service employees is not based on medical acts performed. Furthermore, when evaluating the resulting amounts, it should be noted that gross earnings from work differ between EU countries. Spain is 13th in the ranking of the 28 EU countries, both in hourly labor costs and in gross average hourly wages [16]. Therefore, we must bear in mind that indirect costs will differ in other countries. Besides, direct costs could also differ between EU countries, with the result that these figures are valid only for costs in the country where this study was carried out (Spain). Notwithstanding, the study can serve as an approximation for other countries and provide a global idea of the costs.

In conclusion, our prospective study systematically evaluated the direct and indirect health care costs of assessing hypersensitivity to RCM in an outpatient clinic showed the cost of a suspected hypersensitivity reaction to be €272.64 (164.77) per patient. Therefore, the costs of an elective evaluation of hypersensitivity to RCM are low, even more so when all the costs of imaging procedures are taken into account. Correct and safe management of patients affected by hypersensitivity to RCM is cost-effective. Efforts should be directed toward implementing the necessary allergy studies, particularly considering that hypersensitivity reactions to RCMs are increasingly frequent.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ **Francisco Javier Muñoz Bellido**

E-mail: fjmbellido@saludcastillayleon.es