Original Article

Immediate hypersensitivity reactions to iodinated contrast media despite drug prophylaxis—a comparative retrospective cohort study of breakthrough reactions in Bern (Switzerland) and Seoul (South Korea)

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Background: Although several studies deal with breakthrough reactions (BTRs) in patients with contrast media (CM) hypersensitivity reactions, the phenomenon is still unclear. Therefore, this study aimed to analyse in depth patients with BTR in two countries.

Methods: We retrospectively analysed the electronic medical records of in- and outpatients (random sample enrolment) from two academic hospitals of tertiary care (Seoul/South Korea, with a special monitoring system exclusively for CM hypersensitivity, and Bern/Switzerland, manually operated) with respect to basic epidemiological data, number of BTRs per patient, and severity grades of severity in follow-up analyses. The study period lasted from 2013 (2000 Bern) to 2017.

Results: We identified 445 BTR-patients (91.5% from Seoul) with 691 BTRs (94.5% from Seoul). Most reactions were mild, 11% moderate and 3.9% severe. In Seoul, we found patients with up to 10 BTRs, and in Bern, there were only patients with one BTR. Fatal reactions or deaths did not occur. In most cases, the severity of the BTRs and of the index reactions were identical (80.8%). Mild index reactions remained constant in 90.6%. In contrast, in moderate index reactions the severity decreased/remained identically in 86.8% and increased in 13.2%. In severe index reactions, 55.6% of BTR reactions were severe again, in 44.4% the severity decreased. In 158 BTRs (22.9%) the culprit iodinated contrast medium (ICM) of the index reaction induced the BTR. In the other 482 BTRs (69.8%) the culprit ICM was changed to another non-culprit ICM.

Conclusions: To the best of our knowledge, this is the largest study on patients with BTRs, and the first study showing BTRs in two centers in two countries of two continents. The main differences between the two centers result from the different hospital size, the number of patients, and the different documentation

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[manual (Bern) *vs.* electronical screening (Seoul)]. BTRs are no contraindications for further ICM-application. We recommend performing an allergy skin test as basis for the decision-making process of the next contrast-enhanced image-guided examination.

Keywords: Breakthrough reaction (BTR); iodinated contrast medium (ICM); hypersensitivity reaction; premedication

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Introduction

Currently, contrast media (CM) are among the most frequently administered intravenous pharmaceuticals. Although the exact number of iodinated CM (ICM)-doses is unknown, it is tempting to speculate that several hundred million doses are given annually (1). CM are safe drugs. Approximately 2% of patients acquire hypersensitivity reactions (2). Despite the low incidence of hypersensitivity reactions, due to the frequency of use, there are likely 2 million reactions annually.

Since patients with a history of a previous CM-hypersensitivity reaction are at increased risk to react again upon re-exposure, special prophylactic management is often administered. Most commonly, such cases receive a premedication with anti-allergy drugs. Unfortunately, currently used premedication protocols have several limitations, such lack of standardization, risk of causing adverse reactions, and inability to suppress the immediate ICM-hypersensitivity reaction (3,4). The latter phenomenon, called breakthrough reaction (BTR), is an adverse reaction following CM-injection despite the application of a premedication (5-7).

Our main goal is the comparison of immediate hypersensitivity reactions despite premedication with H1-Blocker and/or glucocorticosteroids (BTR) of two capitals from technologically advanced countries. Through this comparison, we can identify different results with BTRs and BTR tracking. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-912/rc).

Methods

BTR-definition and study population

We retrospectively analysed patients with BTRs from two academic clinical centers (multi-center study), one center in Seoul, South Korea, and the other in Bern, Switzerland (cohort study). We included only immediate reactions [hypersensitivity reactions that occur during and up to one hour after the ICM-injection (8)], and BTRs due to ICM. We defined BTRs as adverse reactions occurring following the application anti-allergy premedication (e.g., H1-receptor antagonist and/or glucocorticosteroids) in patients with a history of a previous adverse reaction to CM. The following three premedication regimens (given as intravenous injection) were used in Seoul 4 mg chlorpheniramine or (I) 40 mg methylprednisolone or (II) 4 mg chlorpheniramine plus 40 mg methylprednisolone and in Bern two premedication regimens were used: (I) 2 mg clemastine (Tavegyl®) or (II) 2 mg of clemastine (Tavegyl®) plus 125 mg of methylprednisolone (SoluMedrol®).

We injected the corticosteroid approximately one hour and the antihistamine drug 15 or 30 minutes prior to CM-injection. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

In addition to basic data (e.g., sex, age), we documented the following facts:

- Index reaction/BTR: date of reaction, culprit CM, premedication (drug, dose), severity grade, and clinical symptoms. Index reaction is defined as initial hypersensitivity without premedication.
- BTR follow-up: re-exposure to CM following the BTR, presence or absence of further reactions, omission of CM, premedication, use of non-culprit CM, changing the imaging modality.

Databases, search algorithms, and study design

Initially, we retrospectively evaluated the institutional electronic radiological database or radiological information

system (RIS): from 2013 to 2017 in Seoul (South Korea) and from 2000 to 2017 in Bern (Switzerland).

The center in Seoul has its own real-time mandatory monitoring system and related database for BTR documentation of BTRs (CosM^{2}oS). This system allowed the extraction of the detailed record of patients with BTR events in the past.

In contrast, at the institute in Bern the term 'BTR' is not yet established in clinical radiological routine. Therefore, we screened for other keywords and phrases such as "CM-allergy despite of a premedication", "acute adverse reaction despite of anti-allergy pre-treatment", "despite the application of Tavegyl®/SoluMedrol® an adverse reaction occurred".

Severity of hypersensitivity reactions

Both index reaction and BTRs were classified (mild: grade 1; moderate: grade 2; severe: grade 3) according to previously published grading systems with minimal modifications (5,8,9) (Table S1).

Post-BTR prophylaxis

Patients who re-admitted to the department following their BTR(s) were also analysed. We categorized the patients according to the documented prophylactic consequences as follows:

- ❖ Naïve (non-contrast) scan;
- ❖ Premedication only;
- ❖ Omission of the culprit CM;
- ❖ Omission of the culprit CM and premedication;
- ❖ Use of another imaging modality;
- ❖ No special prophylaxis.

Statistical analysis

Data are expressed as mean ± standard deviation (SD), if not otherwise indicated. We proved the normal distribution of the investigated cohorts by the Kolmogorov-Smirnov test. Significance of differences between means was calculated using the Student's *t*-test, the Wilcoxon, the Mann-Whitney-U test, the Chi-square test or the Fisher's exact test. We calculated odds ratios (ORs) and their 95% confidence intervals (95% CI) and made comparisons between the indicated groups. Statistical significance was defined as a two-tailed P value <0.05. We used R, 4.1.0, R Core Team, Vienna, Austria, as statistic software.

Results

Comparison between Seoul and Bern

We retrospectively identified 445 patients (men n=196) with a mean age of 54.4 years (±12.6 years) who experienced 691 immediate BTRs (*Table 1*). Although the period of the analysis was longer in Bern (17 versus 5 years), the number of retrieved patients was ten times greater (407 versus 38), and the number of BTRs was 17 times greater in Seoul (*Table 1*). Patients with a history of one BTR dominate in the analysed cohort.

In Bern, we used mainly H1-blocker plus corticosteroids as premedication, while Seoul mainly used H1-blockers only for cases with mild index reaction and H1-blockers plus corticosteroid for the cases with moderate or severe reaction. The combination H1-blocker plus corticosteroid was applied in 213 cases, while 474 cases received a H1-blocker only.

The number of mild index reactions (n=584) is very similar to the number of mild BTRs (n=586). The quotient of moderate index to moderate BTR is 1:1.1 and the quotient of severe index to severe BTR is 1:1.5. Overall there are slightly more moderate and severe BTRs than index reactions. We should realize that the subgroup with unknown severity in the index reaction is higher, and therefore, a comparison should be done with caution.

All patients in Bern experienced BTR once, whereas, 281 patients (69%) experienced BTR once, and two patients (0.5%) experienced BTR up to 10 times in Seoul (Table S2). They were in most cases mild (n=586), and the severity of the reaction mostly corresponded the index reaction (n=558).

We identified the following culprit ICM of index reactions: iohexol induced most index reactions (with n=214, 31%), and was followed by iopromide (n=149, 21.6%) and Iobitridol (n=118, 17.1%) (*Figure 1A*). We rarely found ioversol as culprit ICM of index reactions (n=18, 2.6%), but more often as responsible ICM of BTRs (n=98, 14.2%). On the other hand, iopromide was often the culprit ICM of index reactions (n=149, 21.6%), but rarely of BTRs (n=79, 11.4%). In South Korea in particular, iohexol, iopromide, iopamidol and iobitridol are used initially (*Figure 1A*), and then the colleagues switched to iohexol, iobitritdol and ioversol for follow-up investigations (*Figure 1B*). For example, 95 patients switched to ioversol.

Grades of severity

As shown in *Table 1*, most reactions were mild. Next, we

Table 1 Epidemiological basics, and characteristics of immediate BTRs in Seoul (South Korea) and Bern (Switzerland) following the application of ICM

Parameter	Seoul (South Korea)	Bern (Switzerland)
Study period	2013–2017	2000–2017
Absolute number of patients	407	38
Absolute number of BTR events	653	38
Male:female (ratio)	177:230 (1:1.3)	19:19 (1:1)
Age (when the first BTR occurred), years	54.7±11.7	56.4±17.6
Premedication (BTR events)		
H1-blocker and corticosteroid	181 (27.7)	32 (84.2)
H1-blocker	468 (71.7)	6 (15.8)
Corticosteroid	4 (0.6)	0 (0)
Number of BTRs/patient		
BTR once	281 (69)	38 (100)
BTR twice	73 (17.9)	0 (0)
BTR multiple	53 (13)	0 (0)
BTR severity		
Mild	563 (86.2)	23 (60.5)
Moderate	64 (9.8)	12 (31.6)
Severe	26 (4)	1 (2.6)
Unknown	0 (0)	2 (5.3)
Index severity		
Mild	573 (87.7)	11 (28.9)
Moderate	64 (9.8)	5 (13.2)
Severe	16 (2.5)	2 (5.3)
Unknown	0 (0)	20 (52.6)
Severity index reaction *vs*. BTR		
Identical	549 (84.1)	9 (23.7)
More severe	60 (9.2)	4 (10.5)
Less severe	44 (6.7)	3 (7.9)
Unknown	0 (0)	22 (57.9)
BTR induced by		
Culprit ICM	150 (23)	8 (21.1)
Non-culprit ICM	481 (73.7)	1 (2.6)
Unknown ICM	22 (3.4)	29 (76.3)

Data are presented as n (% or ratio) or mean ± standard deviation. The data is presented as number of patients or BTRs in the examined subgroup and in blankets the frequency compared to the absolute number of patients or BTR events in Seoul or in Bern (if nothing else is declared). BTRs, breakthrough reactions; ICM, iodinated contrast media.

compared BTR-patients with mild and moderate or severe reactions (*Table 2*). Although women had slightly more moderate and severe reactions than men, the difference was not statistically significant. The severity of the BTR and the index reaction was identical in most cases (80.8%) (*Figure 2A*). Mild BTRs had in 90.1% a history of mild index reactions (*Table 2*), but even mild index reactions could also induce moderate/severe BTRs. Usually, moderate/severe index reactions induce BTRs of the same severity. 53.4% of moderate/severe BTRs had a mild index reaction. The combination H1-blocker plus corticosteroid was the preferred premedication in the moderate/severe group.

In the next step, we compared the severities of the index reaction and BTR (*Tables 3*,*4*). We found 90.6% (528 of 583) patients with mild index reactions who again acquired a mild BTR. An aggravation occurs in 9.4% of cases (*Table 3*). Patients with moderate index reactions mainly responded equally or less severely to CM (86.8%) and 13.2% acquired a severe BTR. In 90.2% (587/651) patients with mild or moderate index reaction, we documented an identical or less severe BTR. Only 9.8% of the patients had a more severe BTR. In the group with severe index reaction, 55.6% again acquired a severe BTR (*Table 4*).

In total, 64 patients showed an increase in severity (BTR versus index reaction). In this subgroup, we omitted the culprit ICM in 75% (48/64). In the group with equal or less severity, we found a similar percentage of 71.6% (433/605) in which the culprit ICM was omitted.

The main difference between patients with equal severity (mild index reaction and mild BTR) and with increased severity (mild index reaction and moderate or severe BTR) was the type of premedication (*Table 3*).

Multiple BTRs

Most patients acquired one BTR only (*Table 1*), and a small proportion (0.5%) of patients acquired up to ten BTRs (Table S2). *Table 5* shows that the number of different ICM per patient increases with the number of hypersensitivity reactions per patient. Despite multiple changes of the ICM (up to six times), hypersensitivity reactions were observed again in some patients (n=2) (*Table 5*).

The number of culprit ICM correlated with the number of BTRs (*Table 5*). On the other hand, the severity of the reaction did not increase in parallel with the increasing number of BTRs per patient (*Figure 2B*).

Most of the patients (71.7%) had only one BTR (*Table 1*).

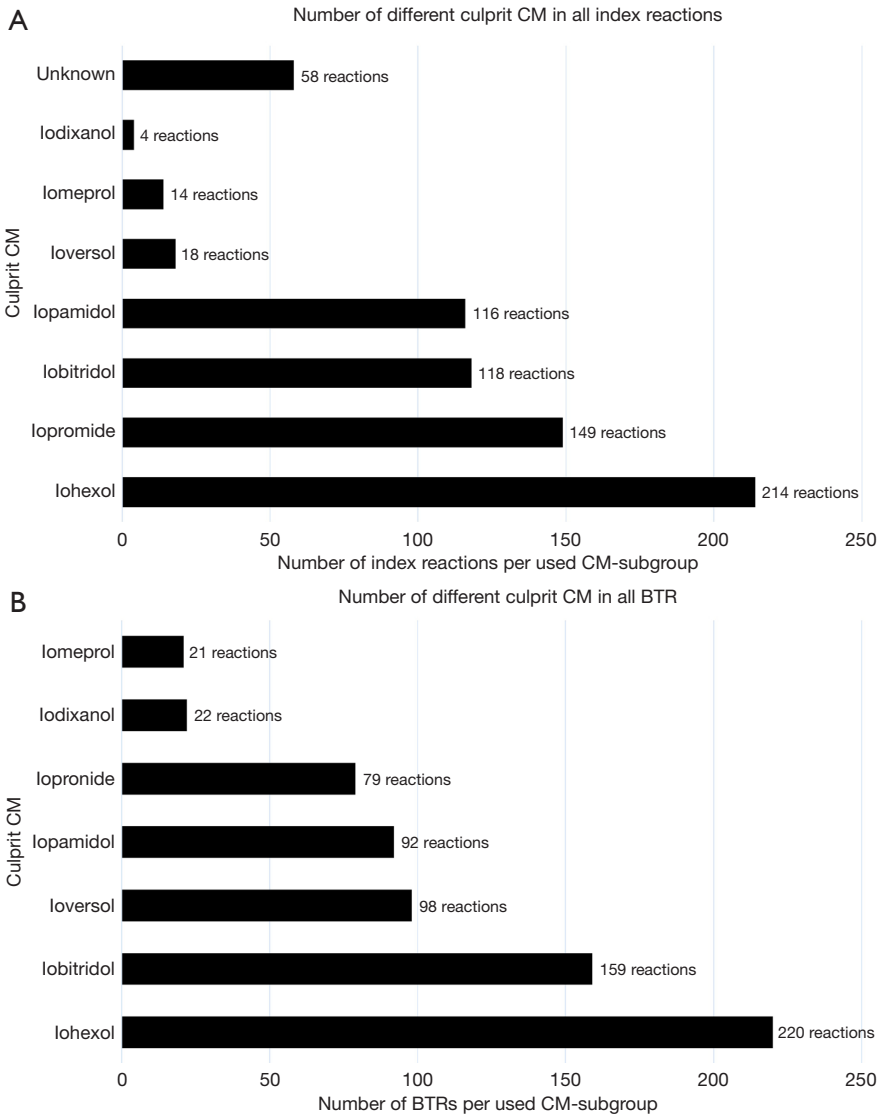

Figure 1 Total number of reactions divided in subgroups of different used culprit ICM (Iodixanol, Iomeprol, Ioversol, Iopamidol, Iobitridol, Iopromide, Iohexol, unknown). (A) Numbers of different used culprit ICM in the index reactions (n=691 reactions). (B) Numbers of different used culprit ICM in BTRs (n=691 reactions). CM, contrast media; ICM, iodinated contrast medium; BTR, breakthrough reaction.

In 126 patients (372 BTRs), we detected two or more BTRs (*Table 1*). Despite multiple BTRs, the severity grade of the BTRs remained in most cases constant (*Figure 2*; see also above under 'Grades of severity'), fatal or lethal reactions did not occur.

Follow-up

Follow-up analyses were possible in a subpopulation of 345 patients (*Figure 3*). In this follow-up analysis, we examine the further course of individual patients after the last BTR included in our study.

In Bern, the prophylaxis led to well tolerated follow-up examinations only. In Seoul, a small subgroup of 31/320 again acquired a hypersensitivity reaction, and the remaining 90.3% of the patients did not show any adverse events. A non-enhanced CT is the safest option that did not induce hypersensitivity reactions. Other prophylactic actions showed that premedication led in 11.1% (8/72), omission of the culprit CM in 12.5% (2/16), omission of

Table 2 Comparison of immediate reactions with different BTR severity grade. We analyzed 689 immediate reactions; 2 reactions were excluded, because the severity was unknown

Parameter	Mild BTRs (n=586)	Moderate/severe BTRs (n=103)	Significance (P value)
Sex, n (%)			0.71
Male	279 (47.6)	47 (45.6)	
Female	307 (52.4)	56 (54.4)	
Index severity, n (%)			<0.001
Mild	528 (90.1)	55 (53.4)	
Moderate	39 (6.7)	29 (28.2)	
Severe	5 (0.9)	13 (12.6)	
Unknown	14 (2.4)	6 (5.8)	
Premedication, n (%)			<0.001
H1-blocker + corticosteroid	154 (26.3)	58 (56.3)	
H1-blocker	429 (73.2)	44 (42.7)	
Corticosteroid	3 (0.5)	1 (1)	

The data is presented as number of BTRs in the examined subgroup and in blankets the frequency compared to the total number of examined BTRs in the column (mild BTRs versus moderate/severe BTRs). BTR, breakthrough reaction.

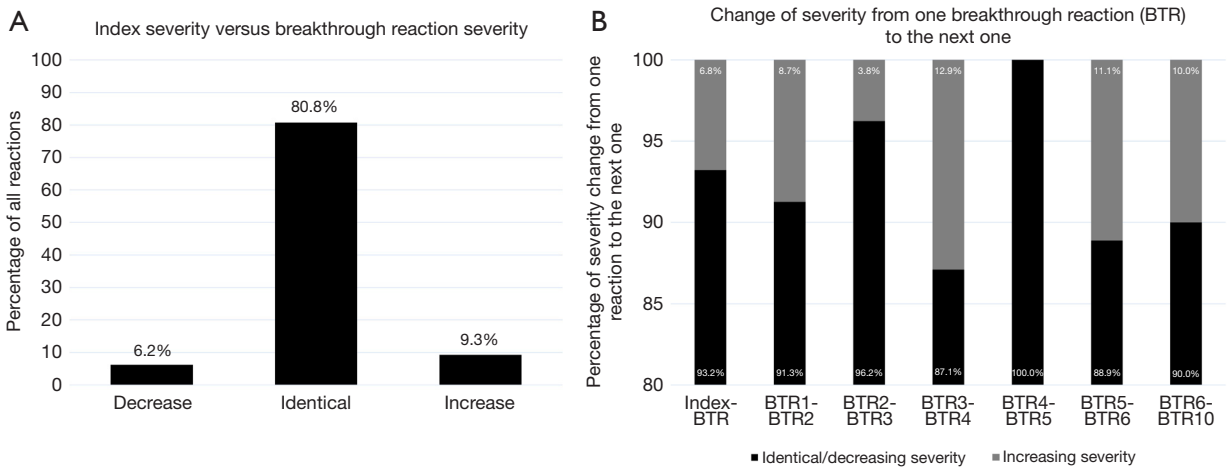

Figure 2 Comparison of the change in the severity in the different reactions. We analysed a total of 669 reactions, 22 were excluded because the severity in one of the reactions was unknown. (A) This graphic shows the comparison between the index reaction severity versus the BTR severity in percentages of increasing (index severity < BTR severity), decreasing (index severity > BTR severity) and identical severity of both reactions (index severity = BTR severity). (B) The graphic shows an overview of the development of the severity grade in all analysed patients with more than one reaction (up to 10 BTRs/patients). The graphic shows the percentages of increasing (previous reaction < following reaction) and decreasing (previous reaction > following reaction)/identical severity of both reactions (previous reaction = following reaction). Total numbers of examined reactions in each column (identical/decreasing severity *vs.* increasing severity): Index-BTR (385 *vs.* 28), BTR1-BTR2 (115 *vs.* 11), BTR2-BTR3 (51 *vs.* 2), BTR3-BTR4 (27 *vs.* 4), BTR4-BTR5 (17 *vs.* 0), BTR5-BTR6 (8 *vs.* 1), BTR6-BTR10 (9 *vs.* 1). BTR, breakthrough reaction.

Table 3 Comparison of immediate reactions with mild index severity grade. We analyzed 583 immediate reactions with a mild index reaction compared to the severity of the BTR

Parameter	Mild index to moderate/severe BTRs	Mild index to mild BTRs	Statistical significance (P value)
Number	55	528	
Male:female (ratio)	25:30 (1:1.2)	248:280 (1:1.129)	0.83
Age, years	55.91±11.7	54.51±11.9	0.88
Index compared to which BTR			0.93
First BTR	33 (60)	329 (62.3)	
Second BTR	11 (20)	99 (18.8)	
Third BTR	3 (5.5)	44 (8.3)	
Fourth BTR	4 (7.3)	24 (4.5)	
Fifth BTR	0 (0)	17 (3.2)	
Sixth BTR	1 (1.8)	8 (1.5)	
Seventh BTR	1 (1.8)	2 (0.4)	
Eighth BTR	1 (1.8)	2 (0.4)	
Ninth BTR	0 (0)	2 (0.4)	
Tenth BTR	1 (1.8)	1 (0.2)	
CM-change			0.21
ICM-change	39 (70.9)	384 (72.7)	
No-ICM-change	12 (21.8)	129 (24.4)	
Unknown	4 (7.3)	15 (2.8)	
Premedication			<0.01
H1-blocker	31 (56.4)	400 (75.8)	
H1-blocker + corticosteroid	23 (41.8)	125 (23.7)	
Corticosteroid	1 (1.8)	3 (0.6)	

Data are presented as n (% or ratio) or mean ± standard deviation. The data is presented as number of BTRs in the examined subgroup and in brackets the frequency compared to the total number of examined BTRs in the column (mild index to moderate/severe BTRs versus mild index to mild BTRs). BTR, breakthrough reaction; ICM, iodinated contrast media.

the culprit CM and premedication in 7.3% (17/233), use of another imaging modality in 25% (1/4), and no special prophylaxis in 33.3% (3/9) to renewed hypersensitivity reaction (*Figure 3*).

Discussion

Although several studies deal with BTRs (6,7,10-21), several aspects of this kind of reactions are far from clear. Our study represents the largest reported cohort of patients with BTRs, with data from two medical centers of two continents.

Although premedication still is one of the main prophylactic measure, its use is questionable (3,21). BTRs show the limitation of premedication. Therefore, we should realise that this kind of prophylaxis is no universal remedy. Even drug schedules with applications over several days did not completely suppress CM-hypersensitivity reactions (7,15,22,23). Moreover, there are adverse reactions (e.g., non-immediate reactions, flush) which cannot be suppressed by a drug pre-treatment (24). Such experiences led to the opinion that patients with BTRs should never again receive contrast materials.

Seoul versus Bern

The most prominent difference is the much greater number of patients and BTRs in Seoul than in Bern (*Table 1*). The

Table 4 Comparison of immediate reactions with different index severity grade. We analyzed 669 immediate reactions; 22 reactions were excluded, because the severity was unknown either in the index reaction or in the BTR

BTR severity	Mild index (n=583)	Moderate index (n=68)	Severe index (n=18)
Mild BTRs			
Total number and percentage	528 (90.6)	39 (57.4)	5 (27.8)
ICM-change	384[a]	25[c]	2[e]
H1-blocker	400	25	0
H1-blocker + corticosteroid	128	14	5
Moderate BTRs			
Total number and percentage	48 (8.2)	20 (29.4)	3 (16.7)
ICM-change	32[b]	11[d]	3
H1-blocker	26	5	1
H1-blocker + corticosteroid	21	15	2
Severe BTRs			
Total number and percentage	7 (1.2)	9 (13.2)	10 (55.6)
ICM-change	7	9	8
H1-blocker	4	3	4
H1-blocker + corticosteroid	2	6	6

The data are presented as number of reactions in the examined subgroup and in brackets the frequency compared to the total number of examined reactions in the column (mild index versus moderate index versus severe index). Unknown: a, 15; b, 4; c, 7; d, 3; e, 1. BTR, breakthrough reaction; ICM, iodinated contrast media.

Table 5 Correlation between number of hypersensitivity reactions (index reaction plus subsequent BTRs) and number of different culprit ICM per patient (for example there are 125 patients with only one ICM in a total of two reactions)

Number of reactions per patient (index and BTRs)	Number of different culprit contrast media per patient					
	1 ICM	2 ICM	3 ICM	4 ICM	5 ICM	6 ICM
2 reactions	125	191				
3 reactions	16	28	29			
4 reactions		8	12	3		
5 reactions	1		3	10		
6 reactions			4	2	2	
7 reactions			2	2	2	
8 reactions						
9 reactions						1
10 reactions						
11 reactions					1	1

BTR, breakthrough reaction; ICM, iodinated contrast media.

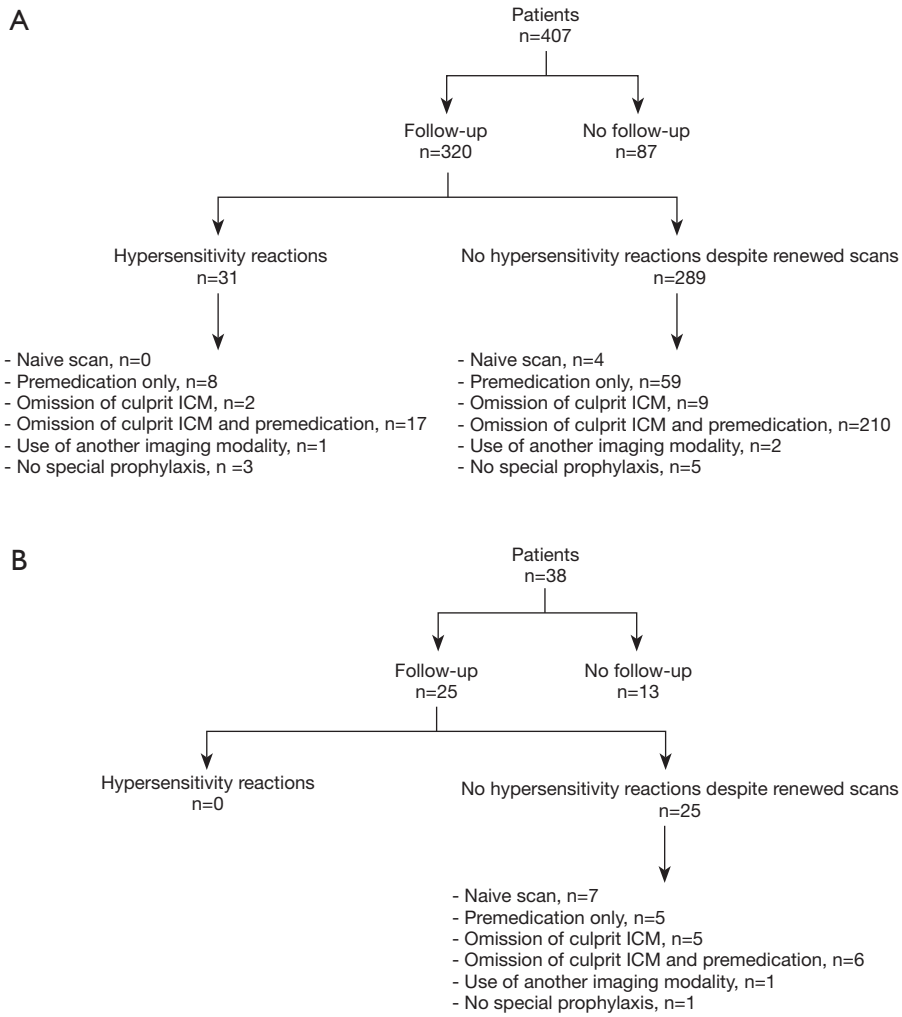

Figure 3 Flowchart showing the post-BTR follow-up in both countries. (A) The flowchart of all included 407 patients from South Korea. (B) The flowchart of all included 38 patients from Switzerland. ICM, iodinated contrast medium; BTR, breakthrough reaction.

reason for this finding could be the specific monitoring system used only in Seoul (see also under Methods). Another possibility could be the size of the population, as well as the number of beds and the number of patients at the two hospitals. Seoul has 10 million inhabitants, and Bern only 130,000. The Seoul National University Hospital has 1,751 beds, approximately 550,000 inpatients and 2.2 million outpatients per year. On the contrary, the University Hospital of Bern only has 893 beds, approximately 45,000 inpatients and 700,000 outpatients. The total number of CT-scans per year in the Seoul National University Hospital is around 270,000, compared to only 20,000 CT-scans in the University Hospital of Bern (25,26).

The premedication used is also different. While patients in Seoul received mainly H1-blockers, in Bern the combination H1-blocker plus corticosteroids is the favoured pre-treatment. Premedication with only corticosteroids or in combination with H1-blockers was the previous preferred drug premedication regiment (7,18,23). Recent papers provide evidence that the use of H1-blockers alone are effective in patients with mild hypersensitivity reactions (17,27,28).

Most patients of Bern had only one BTR. In Seoul, we documented up to ten BTRs per patient. This fact could be due to the much greater number of patients obtained from Seoul. South Korea has the better monitoring system, because they use a special software, and thereby they

improved both the documentation and recruitment.

The severity grade of reactions also showed differences (see also below). Although most patients had mild BTR, the obtained percentage was much greater in Seoul than in Bern (86.2% versus 60.5%). The comparison of index reactions and BTRs show that the severity grades were identical in most cases, but the calculated percentage was greater in Seoul than in Bern. We should realize that the subgroup with unknown severity is higher in Switzerland. Therefore, a comparison should be done with caution.

Grades of severity

As mentioned previously (6,7), in most instances BTRs have the same severity as the index reaction (*Table 4*; *Figure 2A*).

In addition, we should realize that in a small percentage of patients the severity could increase (*Figure 2A*). We observed in 1.2% (7/583) of the patients with a mild index reaction and in 13.2% of patients with moderate index reaction severe BTRs (*Table 4*). An increase in the severity of the reaction should result in an allergy analysis (skin testing) as a basis for the decision-making process of the next contrast-enhanced image-guided examination (4,22).

Although the omission of the culprit ICM is an effective prophylaxis, we observed in 67.4% of patients with moderate or severe index reactions, BTRs despite the change to a non-culprit ICM (*Table 4*). Therefore, ICM application following a moderate index reaction should be performed with caution. In these patients and in those with severe index reaction, an allergy skin testing should be performed before the patient is given another ICM. We found that 72.2% of patients reacted with a moderate or severe BTR despite premedication and change of the ICM (*Table 4*). Patients with aggravation during their follow-up seem to have special, yet unknown conditions. Moreover, on our data it was not possible to find them. Therefore, further (prospective) studies in future are necessary to solve this problem.

As shown, different prophylactic actions led to different percentages of renewed hypersensitivity reactions (*Figure 3*).

An acceptable pretreatment option in patient with mild index reactions is the omission of the culprit CM, and the application of another non-culprit CM. In patients with moderate or severe index reactions we recommend an allergy work-up, because BTRs occurred despite premedication and ICM change. Thereby our data support previous papers (17,27,29,30).

Multiple BTRs

In the group of South Korea, we documented up to ten BTRs per patient. Therefore, it becomes clear that these patients reacted against (nearly) all the ICM applied (*Table 5*). A subgroup of seven patients acquired a minimum of six BTRs (Table S3). Although these patients had an increased number of culprit ICM, only three patients showed an increase of the severity grade. Possible reasons for multiple allergies to different CM molecules may be different contacts with contrast agents (e.g. following the application in radiology, as well as following unknown contact via drinking water) (31). Moreover, reactions against additives of the CM-solution, latex or even the premedication itself could also be possible explanations (32,33).

Limitations

Although we present a great number of patients with BTRs, the study has some limitations. Neither data of Switzerland nor of South Korea were suitable to calculate the incidences of BTRs. The two countries used different methods to retrieve patients with BTRs, either by a special EMR (electronic medical record)-based monitoring system (Seoul) or by a simple manual search strategy (Bern). This could be one of the reasons for the great different number of identified patients. Follow-up data are present in some parts of the study population, and allergy skin tests are missing in the pooled study cohort. It should be realised that independent of the recruitment system, the exact documentation of individual patients is very important and necessary (34).

Recently, it has been shown that a premedication with H1-blockers only is an acceptable pre-treatment option in patients with mild BTR (17,27,28). Due to a lacking control group, we are not able to present data on the efficacy of the drug premedication regimen (combination H1-blocker plus corticosteroid versus H1-blocker only).

Conclusions

The application of the culprit CM plus a premedication is an established procedure, but this type of prophylaxis bears the risk of a BTR. Herein, we for the first time compared BTR-events in two centers in two countries of two continents. Thus, it becomes clear that the main differences resulted from different practises to document such adverse reactions. The principle characteristics were similar.

BTRs are still a challenge in routine radiology practice, but they are no contraindications for further ICM-application in future contrast-enhanced image-guided examinations (18), because (I) even in patients with several BTRs no fatal reaction occurred; (II) in most cases with mild BTRs again mild reactions were observed; (III) an increasing severity was only observed in a minority of patients. But some residual risk for another BTR remains, as shown by our data.

Premedication alone, as well as premedication and ICM change, are not suitable as BTR-prophylaxis. In both countries several patients with a minimum of one hypersensitivity reaction or BTR. Therefore, we recommend an allergy work-up in patients at risk. In patients with mild reactions, the risk of a BTR is small (but present) even without allergy test and is not harmful for the patient. More than 90% of the reactions are mild again [incidence of BTRs in the literature between 1.2–19% (21,35)]. In this context, it is very important that every adverse reaction caused by contrast media is documented exactly. In both countries, renewed exposure to culprit contrast media occurred despite documented culprit ICM. This is because it was previously believed that hypersensitivity reactions to ICM were triggered by iodine (1,30).

The role of other prophylactic actions such as desensitization (36,37) or use of low contrast doses and/or low injection speed as mentioned previously (38), remains to be elucidated in future prospective studies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-912/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-912/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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