Patients' oral hydration levels and incidence of immediate to short-term mild side-effects in contrast agent enhanced MRI diagnostics

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**Abstract**

Aim: Gadolinium-based contrast agents for radiodiagnostic purposes can lead to side effects, including nephrotoxicity in patients with renal insufficiency. This study evaluated whether the occurrence of mild side effects from gadolinium-based contrast enhanced magnetic resonance imaging (MRI) correlates to patients' oral hydration levels.

Methods: Oral fluid intake levels 24 h pre- and 24 h post-MRI, as well as incidence of mild side-effects experienced 30 min and 24 h post-MRI were recorded by using a patient self-reporting questionnaire. Results: A total of 174 patients, 29 controls, 98 administered Prohance and 47 receiving Dotarem, were enrolled. Overall, the most frequently reported side-effect was headache; nausea only occurred in pa-tients receiving contrast agent. One or more side-effects experienced 24 h following the MRI scan were reported by 10% (controls), 24% (Prohance) and 22% (Dotarem) of patients, respectively. Multivariate ordinal regression analysis showed that only male gender (OR 0.24, 95% CI 0.11e0.53) was statistically significantly associated with a decreased incidence of side-effects 30 min after MRI. At 24-h post MRI, a lack of contrast agent (OR 0.40, 95% CI 0.09e1.74) and male gender (OR 0.46, 95% CI 0.19e1.09) were associated with fewer side-effects.

Conclusions: The level oral fluid intake before and after undergoing gadolinium-based contrast-enhanced MRI does not appear to markedly affect the incidence of common undesirable mild symptoms experienced shortly after the procedure. Confounding differences between patients in reporting side-effects may contribute to these findings.

**Introduction**

The use of magnetic resonance imaging (MRI) as a diagnostic tool has risen dramatically and is being further developed all the time.[1](#bookmark6)e[3](#bookmark6) Worldwide, the majority of MRI contrast enhanced pro-cedures are performed with contrast agents based on chelates of the paramagnetic ion gadolinium.[4](#bookmark7) In patients with severe renal function impairment, the use of gadolinium carries the risk of nephrogenic systemic fibrosis (NSF).[5](#bookmark8)e[7](#bookmark8) Other non-renal adverse reactions e.g. anaphylactoid reactions, dizziness and nausea can also occur.[8](#bookmark10)e[12](#bookmark10) However, delayed reactions have also been reported, typically appearing 24e96 h after intravenous administration.[13](#bookmark12) Research has focused on reducing the risk of the incidence of adverse events, contrast-induced nephropathy in particular, by

applying patient based exclusion criteria to gadolinium-based contrast enhanced MRI and also by increasing the rate of gadolin-ium excretion out of the body through hydration protocols. In some studies, patients have been subjected to a e intravenous or oral e hydration protocol, with positive outcomes.[14](#bookmark13)e[16](#bookmark13)

The aetiology of reaction rates is unclear but major safety con-cerns about residual chelate and/or the possible release of free gadolinium within the body have been made.17 This study aimed to establish whether increased patient fluid intake reduces the inci-dence of mild side-effects experienced shortly after a contrast-enhanced MRI scan.

Methods

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Ethics

In this prospective, multi-centre, controlled observational study, patients were identified from appointment lists for MRI scans.

Eligible patients were provided with an information leaflet, explained the aim of the study, freedom of choice and invited to participate. Completion and return of the questionnaire was deemed as providing informed consent. The study was approved by the National Research Ethics Service, reference 09/H1015/79, and local Trust permission was obtained at the two participating NHS Trusts; the study was conducted according to principles outlined in the Declaration of Helsinki.

*Patients*

Inclusion criteria were that the patients were aged >18 years and capable of reading and speaking English. Exclusion criteria were renal insufficiency defined as severe renal impairment (ie, GFR [glomerular filtration rate] or eGFR [estimated GFR] <30 mL/ min/1 -73 m2); in patients with renal dysfunction who had undergone, or who were awaiting, liver transplantation[8,13](#bookmark10); referral for a condition with associated symptom(s) identical to those recorded as potential side effect of contrast agent (e.g. referral for chronic dizziness); patients who were required to fast for the MRI examination; patients who were required to have preparation for small bowel studies with pre scan hydration protocols; any patient who did not have the standard MRI contrast dose of 0.1 mmol per kg. Renal function assessment was conducted in line with local clinical guidelines; due to the anonymous nature of the questionnaire, patients' responses could not be matched with renal function results.

Contrast agents

The contrast agents used by the two recruitment sites were Prohance (cyclic, non-ionic) and Dotarem (cyclic, ionic) respec-tively; controls were recruited from the same hospital site using Prohance. No saline or other control substance injection was administered to the control patients.

Both contrast agents were administered at the standard indi-cated dose. MRI scanners were all 1.5 T models.

Questionnaire

Fluid intake, 24 h pre- and 24 h post contrast enhanced MRI, was divided into three ordinal categories: less than 1 L, 1 L to 1.5 L, and more than 1.5 L. Patients who completed the questionnaires were not asked to follow a hydration protocol; it was self-reporting fluid intake that was recorded. Symptoms which participants could select: headache, nausea, dizziness, strange taste, other, numbness in legs, and painful injection site (feeling of coldness, swelling, redness). This is identical to the options offered by Bailey et al.; the ‘numbness in legs’ option was included to establish whether pa-tients exhibited acquiescence bias[16](#bookmark15)

*Statistical analysis*

Data was collated and analysed using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc. Chicago, IL, USA, 2007). A p-value of 0.05 or less was considered statistically significant.

Results

A total of 174 patients completed and returned a questionnaire. [Table 1](#bookmark0) summarises the demographics of this sample. There was no difference in the mean age and gender ratio in the three sample groups, controls (no contrast agent), Prohance and Dotarem. Three patients in Prohance group did not disclose their gender. The body part under clinical investigation did not differ either, with all three groups containing patients who were being assessed for craniofa-cial problems, liver lesion characterization and musculoskeletal problems. We asked patients to record any side-effects half an hour after the diagnostic assessment. The first time point for assessing the presence of side-effects, was chosen because ESU Guidelines (2012) recommend patients to remain in the radiology department for 30 min after contrast-enhance MRI. The second time point was 24 h after the procedure, and therefore the focus was on immediate to short-term effects of contrast agent. [Table 2](#bookmark2) and [Table 3](#bookmark3) show the incidence of side-effects for 30 min and 24 h post-MRI respectively. Contrast agent administration led to more side-effects; furthermore, nausea was only recorded in patients who were administered a contrast agent. Symptoms recorded under ‘other’ by participants included “shaky, tight chest & epigastric discomfort”, “very mild palpatations”, and “aching in upper arm”.

Through multifactorial ordinal regression analysis the association of the following factors with the incidence of side-effects post-MRI was explored. At 30 min, the only factor significantly associated with a decrease in side-effect reporting was male gender. The decrease in side-effects reported in control patients was not significant compared to patients receiving contrast agent and the level of oral fluid intake did not have a bearing on the incidence of undesirable effects either (see [Table 4](#bookmark5)). A similar picture emerged for ordinal regression analysis of 24-h post-MRI data, see [Table 5](#bookmark4). None of the factors were significantly linked to the incidence of side-effects, however there was a trend for: control patients and males to report fewer side-effects; patients under the age of 60 and those consuming less than 1.5 L of fluid orally (24 h before the MRI-scan) to report more side-effects.

Discussion

ESUR guidelines recommend increased fluid intake to minimise the risk of adverse event after contrast-enhanced imaging.[8,13](#bookmark10) As Ten Dam & Wetzels[6](#bookmark9) point out, there is actually very limited evi-dence from studies to support this recommendation. Only one study by Trivedi et al.[18](#bookmark16) has compared a saline hydration protocol with placebo in radiological examination using iodinated contrast agents. Various studies have since supported the use of intravenous hydration protocols in patients who will be administered iodinated contrast media.[6](#bookmark9)e[8](#bookmark9) The results in our study differ from those pre-sented by Bailey and colleagues,[16](#bookmark15) who showed that a non-randomised oral hydration protocol e consisting of 2 L of clear fluid intake both 24 h before and 24 h after the MRI appointment e reduces the symptom rate 24 h post MRI from 41% in controls (24 out of 58 patients) to 14% in those that followed the hydration protocol. In Bailey's study, patients reported to a researcher over the telephone, whereas in the present study patients reported in writing. Furthermore, we took a multivariable analysis approach, to take into account potential confounding factors. From this we show that females appear to report more side-effects than male patients. A similar outcome has been observed in other studies too, both conducted in an Asian population.[11 ,1 2](#bookmark11) Some limitations of this study include: this is not a randomised controlled trial of a hy-dration protocol. On the one hand it makes it harder to quantify the true effect of increased hydration levels on symptoms experienced by patients undergoing gadolinium-based contrast enhanced MRI. On the other hand, this does give an insight into real-life hydration levels of patients who attend for MRI in two general district hos-pitals, and an overview of patient-reported symptoms following their MRI. In our study, approximately 40% of patients consumed more than 1.5 L of fluids both before and after the MRI; the dif-ference between 1.5 ltr and the specified 2 L of fluids recommended in the hydration protocol by Bailey and colleagues may contribute to the discrepancies seen in mild side-effect incidences between this study and theirs.[16](#bookmark15) As in Bailey's study, participants in the present study reported more adverse effects than for example in the clinical trial involving Dotarem and percentages reported in other studies.[18](#bookmark16)e[20](#bookmark16) The self-reporting method may have contributed to this discrepancy.

In this study we focussed on mild to moderate symptoms re-ported by the participants. Mild effects can also occur due to the MRI procedure itself, rather than contrast agent; dizziness being such a manifestation, and indeed observed in both control and contrast agent patients. Life-threatening adverse events such as NSF are reported to occur several days after undergoing the pro-cedure and its incidence is 0.0003%e0.0175.[21](#bookmark17) Nonetheless, in some radiology units, patients may leave the imaging department mi-nutes after completion of their examination despite recently pub-lished ESUR guidance recommended; this is potentially a cause for concern given that it is not uncommon for patients to experience e.g. dizziness & nausea, as reported here and byothers.[15](#bookmark14) In terms of avoidance of the incidence of NSF, the application of stringent eligibility criteria, exclusion of patients with significant renal impairment, and maximum dose limits, 0.3 mmol/kg body weight, remains the core strategy.[8,13](#bookmark10) Asking patients to increase their fluid intake generally speaking is not likely to cause any adverse effects by itself, apart from in people with e.g. cardiac failure.[8,13](#bookmark10) Since an isotonic saline solution is more effective for reduction of adverse events in iodinated radiodiagnostics,[6,22](#bookmark9) the introduction of a saline-based oral hydration protocol could possibly be considered e particularly for patients at higher risk of developing NSF.

In conclusion, the introduction of an oral hydration protocol in patients who are undergoing gadolinium-based contrast enhanced MRI and who do not have impaired kidney function is unlikely to result in a marked reduction in mild side-effects. However, there likely to be no harm in advising patients to drink plenty clear fluids in line with WHO guidelines.[23](#bookmark18)

Conflict of interest statement

None of the authors have any conflicts to declare.

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Table 1

Patient demographics.

Control (no contrast agent) Prohance (non-ionic) Dotarem (ionic) p-Value

n 29 98 47

Age (mean, yrs) 56 53 53 0.494a

Males/Females (n);%Male 15/14;52 43/52;45 20/27;43 0.734[b](#bookmark1)

Top three of main body parts Craniofacial (7), prostate (5), Shoulder (12), craniofacial (9), Craniofacial (15), spine (6),

investigated (n) knee (3) spine (6) hip (3)

a One-way analysis of variance. b Chi-square test.

Table 2

Symptoms reported by patients, 30 min post-MRI.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Control (n) | Prohance (n) | Dotarem (n) |
| Total patients (n) | *(29)* | *(98)* | *(47)* |
| No symptoms | 79% (23) | 70% (69) | 66% (31) |
| One symptom | 14% (4) | 18% (18) | 26% (12) |
| Two or more symptoms | 7% (2) | 12% (11) | 8% (4) |
| Total number of symptoms | *(10)* | *(29)* | *(20)* |
| Headache | 40% (4) | 34% (10) | 40% (8) |
| Nausea | 0 | 14% (4) | 10% (2) |
| Dizziness | 30% (3) | 21% (6) | 25% (5) |
| Strange taste | 20% (2) | 21% (6) | 20% (4) |
| Numbness in legs | 10% (1) | 3% (1) | 0 |
| ‘Other’, related to injection | 0 | 7% (2) | 5% (1) |

Table 3

Symptoms reported by patients, 24 h minutes post-MRI.

Symptom

Control (n) Prohance (n) Dotarem (n)

Total patients (n) (29) (99) (46)

No symptoms 90% (26) 76% (75) 78% (36)

One symptom 10% (3) 16% (16) 18% (8)

Twoormore symptoms 0%(0) 8%(8) 4%(2)

Total numberofsymptoms (3) (35) (13)

Headache 100% (3) 37% (13) 46% (6)

Nausea 0 17% (6) 31% (4)

Dizziness 0 14% (5) 0

Strange taste 0 11% (4) 8%(1)

Numbnessinlegs 0 9%(3) 8%(1)

‘Other’, relatedtoinjection 0 11% (4) 8%(1)

Table 4

Multivariable ordinal regression analysis for the association of factors with adverse

effects 30 min after MRI.

Variable

Category

N%

p-Value Odds ratio 95% CI

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patients | Total sample size | 170 | 100 |  |  |  |
| Group | Control | 29 | 17.1% | 0.33 | 0.56 | 0.18 to 1.77 |
|  | Prohance | 94 | 55.3% | 0.54 | 0.77 | 0.34 to 1.77 |
|  | Dotarem | 47 | 27.6% | e | 1 | e |
| Fluid 24 h | Up to 1 ltr | 35 | 20.6% | 0.70 | 0.82 | 0.31 to 2.20 |
| before MRI | 1 to 1.5 ltr | 69 | 40.6% | 0.44 | 0.73 | 0.32 to 1.64 |
|  | More than | 66 | 38.8% | e | 1 |  |
|  | 1.5 ltr |  |  |  |  |  |
| Age | Under 30 yrs | 31 | 18.2% | 0.97 | 0.97 | 0.25 to 3.70 |
|  | 30e39 | 31 | 18.2% | 0.60 | 1.42 | 0.38 to 5.30 |
|  | 40e49 | 37 | 21.8% | 0.70 | 1.29 | 0.35 to 4.65 |
|  | 50e59 | 48 | 28.2% | 0.84 | 0.87 | 0.24 to 3.14 |
|  | 60 plus | 23 | 13.5% | e | 1 | e |
| Gender | Male | 77 | 45.3% | <0.001 | 0.24 | 0.11 to 0.53 |
|  | Female | 93 | 54.7% | e | 1 | e |

An odds ratio below 1 is associated with decreased incidence of adverse events, whereas an odds ratio above 1 indicates an association with increased adverse events post-MRI.

