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**MRI-CASE study - A controlled study comparing effects of patient hydration protocol vs standard practice for MRI diagnostics involving contrast agents.**

#### **Abstract**

It is well documented that contrast agents for radiodiagnostic purposes can lead to side effects. Administration of contrast agents can cause nephrotoxicity in patients with renal insufficiency. In this study we aim to investigate whether or not a hydration protocol helps to avert the occurrence of side effects from contrast agents administered for MRI diagnostics.

Patients will form part of a control group, in which patients are not given any advice on fluid intake or hydration levels, or they will be part of a group of patients asked to consume two litres of clear fluids prior to contrast agent administration and undergoing a MRI scan, and two litres of clear fluids following the scan. Both groups will be asked to complete a questionnaire to register if participants have experienced any adverse effects related to contrast agent administration. Two timepoints are checked: 30 minutes and 24 hours following the MRI scan, respectively. The outcomes in both groups will be compared to assess if additional fluid intake can minimise the risk and prevalence of developing side effects when having a MRI scan with contrast agent.

#### **Aims and objectives**

To establish what the outcome will be of hydrating a patient prior to and post contrast agent enhanced MRI in terms of side effects associated with the administered contrast agent.

#### **Methodology**

This trial will measure the incidence of side effects in patients who are administered contrast agent (CA) for a CA-enhanced MRI scan.

We will independently investigate - ie not compare against each other - three different contrast agents commonly used in CA-enhanced MRI scanning: Prohance, Dotarem

and Gadovist. For each agent, two arms will exist, a control group and an intervention group.

The intervention is essentially uptake of extra clear fluids by the intervention group (also called hydration group).

The protocol for this – for the purpose of this trial – is as follows:

- Prior to administration of contrast agent and MRI scan

Two litres of clear fluids\* over a period of 24 hours.

- Following MRI scan

Two litres of clear fluids\* over a period of 24 hours.

\* Clear fluids means water or diluted cordial/fruit juice. No alcoholic beverages, carbonated drinks, caffeinated drinks such as coffee or tea, concentrated fruit juices or milk-based drinks

This means that there will be six different groups in total. Participants will be not be randomised (i.e. allocated to one of two groups by chance) for allocation into the control or intervention group. Instead, the control group will be recruited first, followed by the hydration group. Each group is recruited prospectively. The choice of contrast agent is predetermined, because the three NHS Trusts that will be recruiting patients all use different types of contrast agents.

Measurement of the incidence of side effects will be done by asking the participants to complete a simple questionnaire both 30 minutes and 24 hours after having the contrast agent administered/undergoing the MRI scan.

### Potential Impact

A previous pilot study that I co-published (Bailey et al, 2007) has already shown promising results in terms of the reduction of side effects experienced by patients who follow a hydration protocol. This study has been designed to be more powerful (power calculation available upon request) in detecting whether hydrating a patient can indeed lead to a significant reduction in the incidence of side effects associated with the administration of contrast agent.

This study involves three different NHS Hospital Trusts: North Cumbria University Hospitals NHS Trust (Cumberland Infirmary, Carlisle), East Lancashire NHS Trust (Burnley General Hospital, Burnley) and Morecambe Bay Hospitals NHS Trust (Royal Lancaster Infirmary, Lancaster). By chance, possibly due to financial reasons or historic developments, each Trust uses a different type of contrast agent for contrast agent-enhanced MRI scans. This study can therefore inform whether hydrating a patient is beneficial and if the benefits differ per type of contrast agent. The outcomes may be used by the three abovementioned Trusts to potentially change practice and following publication of the results there may well be a more widespread adaptation by different NHS Trusts, depending on what these outcomes will be. At this stage we cannot make assumptions whether hydration is beneficial per se, but if it does prove to be then patients would benefit from introducing it into standard practice.

### Outcomes

Incidence of side effect(s) experienced by participants, at 30 minutes and 24 hours after administration of the contrast agent, respectively, following contrast agent enhanced MRI scan. This study will assess the patients for immediate and delayed side effects which are reported by the manufacturers and literature to be present in 1% or above of patients.

- Headache
- Nausea
- Dizziness
- Strange taste
- Numbness in the legs - N.B. The questionnaire will contain one question regarding numbness in the legs, which is not a documented side effect of gadolinium based contrast agent injection. This was placed on the questionnaire to see whether patients exhibited acquiescence bias (Bowling 1997), demonstrating a psychosomatic response due to questionnaire construction (Marshall 1996) which could jeopardise the validity of the data. The OptiMark trial subjects also exhibited acquiescence bias to a dummy question (Brown et al 2002).
- Injection site painful (feeling of coldness, swelling, redness)\*. This type of side effect may be dependant on the expertise of the person administering the contrast agent. Since the three different contrast agents will be applied in three different Trusts by at least three different people, this is not feasible. Therefore, its incidence will be recorded separately from the other side-effects mentioned above.

#### Evaluation and dissemination strategy

As mentioned, three NHS Trusts will be involved in recruiting patients and generating the data. The chief investigator (Prof Marshall), co-investigator (Dr Jonker) will form a committee together with the three principal investigators at the three hospital sites (Dr Jon Berry, consultant radiologist in Carlisle; Mr Chris Kasap, MRI superintendent radiographer in Burnley and Dr Melanie Schofield, consultant radiologist in Lancaster). The MRI-CASE committee will evaluate the outcomes of the study. In addition, they will together be authors on the manuscript that is to be written. The aim is to submit a manuscript to a peer-reviewed scientific journal e.g. Radiography. Further dissemination will take place through presentations at scientific conferences. Internal reports will also be drafted for use in radiology departments of the three NHS Trusts.

#### Timetable

- September 2009:* submission of grant proposal to College of Radiographers
- October 2009:* outcome of ethics committee's opinion regarding MRI-CASE study
- November 2009:* commence recruitment of participants into the 'control' arm of the study. Patients will be asked to complete a questionnaire following contrast agent-enhanced MRI scan without following hydration protocol.
- July - August 2010:* recruitment into control arm finalised and data analysed
- August 2010:* commence recruitment of participants into the 'hydration' arm of the study. Patients will be asked to complete a questionnaire following contrast agent-enhanced MRI scan whilst following a hydration protocol.
- August - Sept 2011:* recruitment into control arm finalised and data analysed

October 2011: manuscript submission to peer-reviewed journal

### Literature Review

Contrast agents are used in 45% of all MRI examinations (Roditi 2009). Early in their use Hughes J et al 2002 asserted that a gadolinium chelate was a safe contrast agent that can even be used in renal failure but ten Cate and Wetzels 2008, Stenver 2008, Broome 2008 state that gadolinium carries the risk of nephrogenic systemic fibrosis (NSF), a potentially lethal disorder occurring in patients with renal failure. Other studies cite acute non-renal adverse reactions e.g. anaphylactoid reactions, dizziness, nausea, pancreatitis and local necrosis of the injection site, as well as acute and delayed renal reactions, which are contrast induced nephropathy and nephrogenic systemic fibrosis respectively ( Bellin and Van der Mole 2008).

Nephrogenic systemic fibrosis was first recognised in 1997 and was first described in the literature in 2000 (Cowper et al 2000). NSF is characterised by the formation of connective tissue in which the skin becomes thickened leading to joint immobility (Cowper, Bucala & Leboit 2006). Patients may develop systemic involvement of other organs and therefore NSF may become a fatal condition (Gibson, Farver and Prayson 2006). Sadowski et al 2007 state a prevalence of NSF 1 in 500,000 for every patient injected. However the American College of Radiologists (2008) suggest that in patients with severe renal disease the risk of NSF is increased to between 1% and 7%.

Crucially NSF has only been reported in patients with renal insufficiency with the majority undergoing dialysis (RCR 2007). The recognition of gadolinium contrast agents as a causative factor of NSF lead to the FDA issuing a warning in June 2006 with subsequent guidelines issued by the MHRA in June of 2007 which form the basis of recognised accepted current best practice in the UK (RCR 2007). The RCR (2007) guidelines placed emphasis on using one of the gadolinium contrast agents not linked to NSF and the lowest dose possible consistent with adequate image quality in patients with end stage renal failure following a careful risk benefit assessment of inducing NSF against denying patients gadolinium enhanced scans which are important for patient management.

In the majority of clinical MRI departments, patients will leave the imaging department shortly after completion of their examination, which is a cause for concern given that it has been shown (Jordan and Mintz 1995) that a proportion of adverse events may occur after the patients have left the hospital premises.

In a pilot study undertaken by Bailey, Marshall and Coals 2007 patients were subjected to either no instructions regarding hydration or a hydration strategy was applied based on a protocol from the European Society of Urogenital Radiology (ESUR) (Thomsen and Morcos 2003), designed to minimize contrast-induced nephropathy following the administration of iodinated contrast agents. The use of this protocol was based on the rationale that increasing diuresis and thus more rapidly eliminating the contrast agent would be beneficial in the reduction of contrast induced reactions. The protocol would result in no deleterious effects given the volumes of water proposed to achieve hydration. This would be provided that patients in whom fluid loading could prove problematic were excluded. The hypothesis for this study was that the hydration regime of the ESUR would significantly reduce adverse events post injection of MRI contrast agents. It was demonstrated that when all immediate and delayed reaction rates were

considered globally there was a statistically different rate of reaction between the two groups. There was a statistically different rate of certain specific delayed reactions namely headache, nausea, dizziness and problems at the injection site between the two groups. This data demonstrated that the hydration protocol used brings about a significant reduction in reactions, which is particularly marked in the delayed reactions. This is a prospective multi-centre, multi-agent trial to provide further evidence

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