



Original Research Article

## Role of Oral Gadolinium as a Negative Contrast Medium in Magnetic Resonance Cholangiopancreatography

Aparna S. Bhatwal<sup>1</sup>, Abhijit M. Patil<sup>2</sup>, Abhimanyu B. Kelkar<sup>3</sup>, Rushikesh A. Naik<sup>3</sup>

<sup>1</sup>Post Graduate Student, Dept. of Radiology, Dr. DYPMC & RC, Pune, Maharashtra, India-411018.

<sup>2</sup>Associate Professor, Dept. of Radiology, Dr. DYPMC & RC, Pimpri, Pune, Maharashtra, India-411018.

<sup>3</sup>Consultant Radiologist, Omega MRI scan centre, Pune-411030.

Corresponding Author: Aparna S. Bhatwal

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### ABSTRACT

In our study, we aimed to evaluate the efficacy of the use of a negative oral contrast agent such as gadolinium - Gd-DOTA (gadolinium-tetraazacyclododecane-tetraacetic acid-meglumine) in MRCP (Magnetic Resonance Cholangiopancreatography) for proper visualisation of the hepatobiliary tree and pancreatic duct. The fluid-filled stomach and duodenum often cause obscuration of the hepatobiliary tree and pancreatic duct. Forty-one consecutive patients, who were referred for MRCP with a clinical suspicion of pancreaticobiliary duct disease, were prospectively examined before and immediately after ingestion of a Gd-DOTA 0.5 mmol/ml solution (1 ml Gd-DOTA). The images obtained before and after the intake of a negative oral contrast agent were studied and compared. We found herein that the contrast agent Gd-DOTA (gadolinium-tetraazacyclododecane-tetraacetic acid-meglumine) constitutes an efficient negative oral contrast agent for MRCP, for it efficiently eliminates the signal of the digestive tube in MRCP images.

**Key words:** oral gadolinium, negative oral contrast, MRCP, pancreatobiliary system.

### INTRODUCTION

In the recent years, MRCP (Magnetic Resonance Cholangiopancreatography) has been accepted as the investigating modality of choice for hepatobiliary and pancreatic duct pathologies as a prominent non-invasive technique. The first description of the use of magnetic resonance imaging (MRI) in detecting dilatation of bile ducts was published by Dooms et al. in 1986, with conventional spin-echo axial MR images weighted in T2 (transverse relaxation time) [1] In 1991, Wallner et al. [2] introduced a non-invasive method for the evaluation of

the anatomy and pathology of pancreatic and biliary ductal system in the form of magnetic resonance cholangiopancreatography (MRCP). Magnetic Resonance cholangiopancreatography (MRCP) is a non-invasive technique that enables visualisation of the pancreaticobiliary ducts with images similar to those obtained with endoscopic retrograde cholangiopancreatography (ERCP). MRCP prevents the need to use an intravenous contrast agent or any intervention in the bile ducts which is the reason why it is considered superior to ERCP. [2,3] However, it has same

contraindications as MRI like patients with cardiac pacemaker, patients with diffuse aerobilia, usually secondary to previous papillotomy or claustrophobic patients. Under these circumstances ERCP is superior to MRCP as the investigation of choice for the detection of choledocholithiasis. Other limitations of MRCP include choledocholithiasis smaller than 4 mm and small pancreatic and periampullary expansile lesions, which are also better diagnosed by echo-endoscopy. [4]

MRCP involves heavily T2-weighted imaging. Regardless of the specific sequences used, MRCP is able to elucidate the anatomy of pancreatic and biliary ducts in one single image which is then available for interpretation instantly. All stationary liquids present a high signal in T2 weighted sequences owing to the projection nature of MRCP images. Hence, the liquids in the interior of the stomach and duodenum overlap the images of the bile ducts and the pancreatic duct, thus, hindering their adequate analysis. In order to prevent this high signal generated by the bowel contents from interfering with the images, patients were required to remain fasting for long durations (8-12 hours) before the scan was done. However, this precaution did not assist a lot in reducing the interference caused by the stomach and duodenum. Hence, the concept of using a negative contrast agent administered orally was tried. [5, 6]

Negative contrast agents use the paramagnetic properties which are intrinsic to the heavy metal ions of some substances. These substances when exposed to an external magnetic field, such as paramagnetic contrast agents, cause an increase in the local magnetic field of the tissue in which they are exposed, reducing T1 and T2, which interferes in signal intensity and, consequently, in contrast of the MR. As there is rise in concentration of substances with paramagnetic properties,

like manganese or gadolinium, T1 signal intensity increases and signal intensity of T2 images reduces. [7] Oral chelated gadolinium-Gd-DOTA (gadolinium-tetraazacyclododecane-tetraacetic acid-meglumine) which is one of the frequently used agents in MRI that is a metallic ion with paramagnetic tendencies which decreases T1 and T2 relaxation time. The ideal oral contrast agent for MR should have a good acceptance by patients, have a uniform distribution in the lumen of the digestive tract, should not be diluted during its transit, should not be toxic, should not stimulate peristalsis, and should have an acceptable cost. [8]

There are anatomic variations in the hepatobiliary tree along with pathologies which can be subtle. The conventional anatomy of right and left hepatic ducts is found only in 57-60% of normal population. [9] Several parts of the proximal GI tract as the stomach and duodenum overlap the hepatobiliary and pancreatic ducts anatomy. In view of the anatomic considerations and subtle pathologies which need high quality and reliable image exam, this study sought to develop a simple methodology to follow anatomic alterations. When Gd-DOTA is administered orally it considerably reduces the interference caused by the bowel contents thereby aiding the better appreciation of anatomic variations as well as diagnosing pathologies. Thus, this study proved that MRCP as a non-invasive investigation can provide images which are of considerably good quality like ERCP which allows accurate and early diagnosis of pancreatic and bile duct disorders.

## **MATERIALS AND METHODS**

The study was performed with a commercially available 1.5 Tesla MR imager (GE Signa Excite) using a phased-array surface coil specifically dedicated to abdominal imaging. Forty-one consecutive

patients, who were referred for MRCP with a clinical suspicion of pancreaticobiliary duct disease, were prospectively examined before and immediately after ingestion of a Gd-DOTA (on table) 0.5 mmol/ml solutions (1 ml Gd-DOTA). Full procedure was conducted in accordance with the recommendations of our Institutional Review Board. Informed consent about the nature and the purpose of the procedure was obtained from all subjects prior to examination. Patients were asked to fast for 4 hours before the examination. The oral contrast was given to the study population in recumbent position on the MR table. Firstly, the axial locator images were obtained. Then the ductal system of pancreas was imaged by applying a single-shot FSE pulse sequence in coronal oblique slab of 40 mm thickness which was placed above the pancreas. The matrix size used for most patients was 256 x 256, the FOV varied from patient to patient but was generally 30 x 30 cm. Echo time was typically more than 750 m sec. The images were obtained while the patient was holding breath. The time required to obtain each section was one to two seconds. This was repeated pre and post administration of oral gadolinium. Additional sequences were respiratory-triggered 3D-MRCP, breath-hold axial T1-weighted in-out phase FSPGR images, breath-hold axial T1-weighted fat-suppressed FSPGR images, breath-hold axial fat-suppressed b-SSFP images.

In order to get unbiased scores, one radiologist who was not part of the statistical analysis gave scores to the images before and after contrast by the following system -

- 1 - High signal intensity from proximal bowel completely obscuring the image
- 2 - High signal intensity from proximal bowel partly obscuring the image
- 3 - High signal intensity from proximal bowel not obscuring the image

4 - No increased signal from proximal bowel

Patient score differences were analysed with the paired t-test with a significant threshold value of  $P < 0.05$ . Scores were applied to the MRCP images obtained from the following structures: (1) CHD - common hepatic duct (2) CBD - common bile duct (3) dCBD - common bile duct - distal part (4) MPD - pancreatic duct of Wirsung. The MPD was analysed in three regions: head (hMPD), body (bMPD) and tail region (tMPD). Differences in visualisation rates for the studied ducts were studied using the chi-squared test (significant threshold value of  $P < 0.01$ ).

## RESULTS

**Table 1 Percentage rates of complete visualisation of the pancreaticobiliary duct parts before and after the use of the negative oral contrast medium (%)**

Part of the ducts	Pre contrast	Post contrast	P value
CHD	61	90	<0.001
CBD	27	81	<0.001
dCBD	17	78	<0.001
hMPD	41	90	<0.001
bMPD	32	87	<0.001
tMPD	29	93	<0.001

**Table 2 Scores given to the images of the structures analysed before and after the use of negative oral contrast medium**

Part of the duct	Pre contrast	Post contrast	Difference	P value
CHD	2.85 ± 0.31	3.34 ± 0.45	0.49	<0.001
CBD	2.71 ± 0.46	3.38 ± 0.47	0.67	<0.001
dCBD	2.03 ± 0.63	2.85 ± 0.75	0.82	<0.001
hMPD	2.37 ± 0.46	3.41 ± 0.55	1.04	<0.001
bMPD	2.42 ± 0.46	3.35 ± 0.59	0.95	<0.001
tMPD	2.15 ± 0.51	3.09 ± 0.61	0.94	<0.001

The quality of images obtained showed remarkable improvement following the intake of oral gadolinium (Figs. 1 to 5) with a statistically significant ( $P < 0.05$ ) score improvement of  $2.025 \pm 0.678$  (mean  $\pm$  SD). Pre-contrast score was  $1.525 \pm$  SD (mean  $\pm$  SD). Post-contrast score was  $3.55 \pm 0.503$  (mean  $\pm$  SD). There were three patients who did not elucidate any improvement of scores in the MRCP images before and after contrast intake (did not remain fasting). The

rates of entirely visualised CHD, CBD, and MPD (head, body, tail) increased significantly ( $P < 0.01$ ) after contrast administration (Tables 1, 2).

Out of the 41 patients that we studied, 23 were found to be normal. However, in these patients also, the distal CBD and pancreatic duct were better visualised after oral gadolinium as in the pre contrast they were obscured by the stomach and duodenum fluids. (Fig. 1)

Of these 23 normal patients, pancreas divisum was promptly visualised in one case after ingestion of oral gadolinium rather than without ingestion of oral gadolinium (Fig. 2).

Of these 23 normal patients, one patient was also diagnosed with mild prominence of the CBD with spasm of sphincter of Oddi. It was possible to rule out other causes of distal CBD obstruction due to proper visualisation of the distal duct following ingestion of oral gadolinium (Fig. 5).

We found four positive cases which were showing chronic calcific pancreatitis with pancreatic duct irregularity and calculi (Fig. 3). The pancreatic duct was partly obscured by the fluids in duodenum and stomach; thus was better visualised on post oral contrast study.

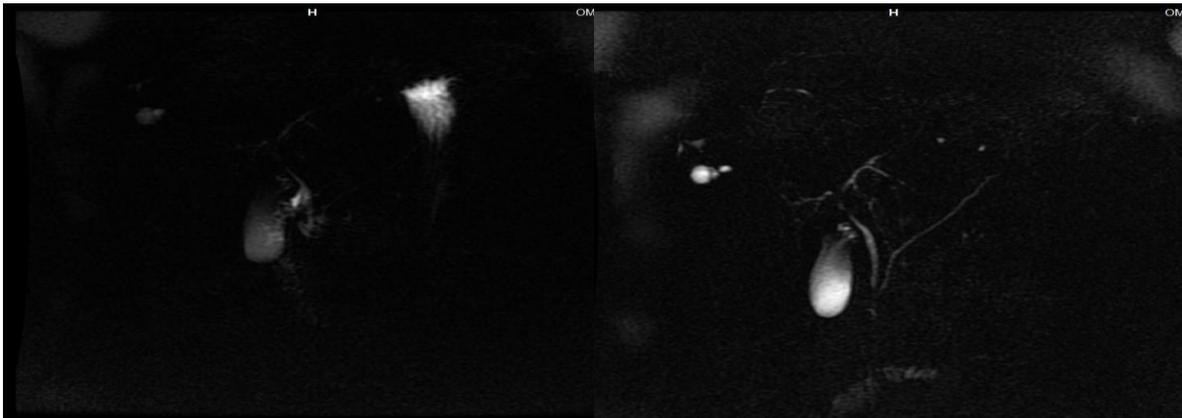


Fig. 1a

Fig. 1b

Figure 1a and b: MRCP images showing normal pancreaticobiliary ducts with pre-oral-gadolinium (1a) and post-oral-gadolinium (1b).

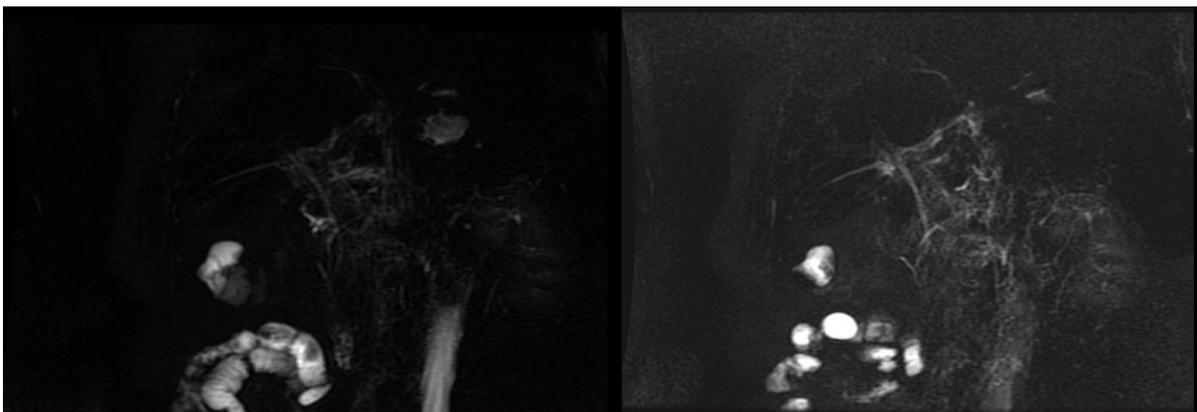
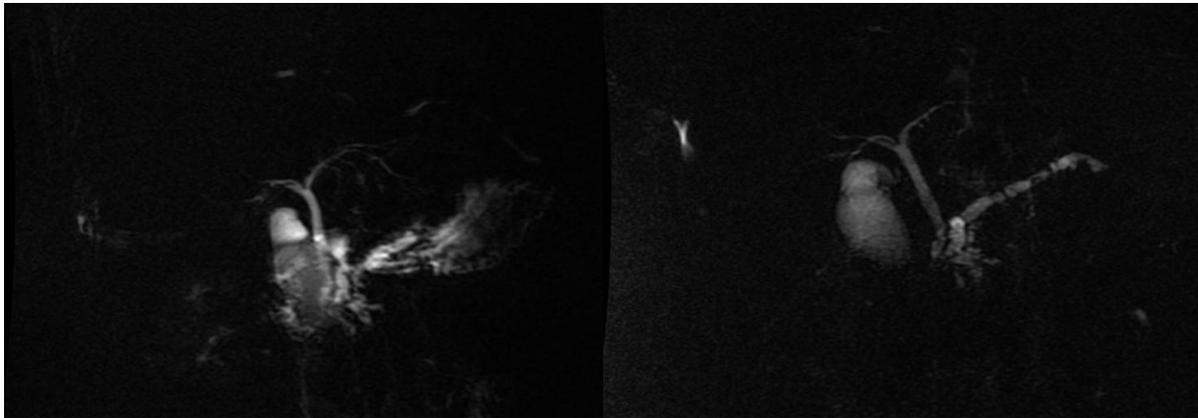


Fig. 2a

Fig. 2b

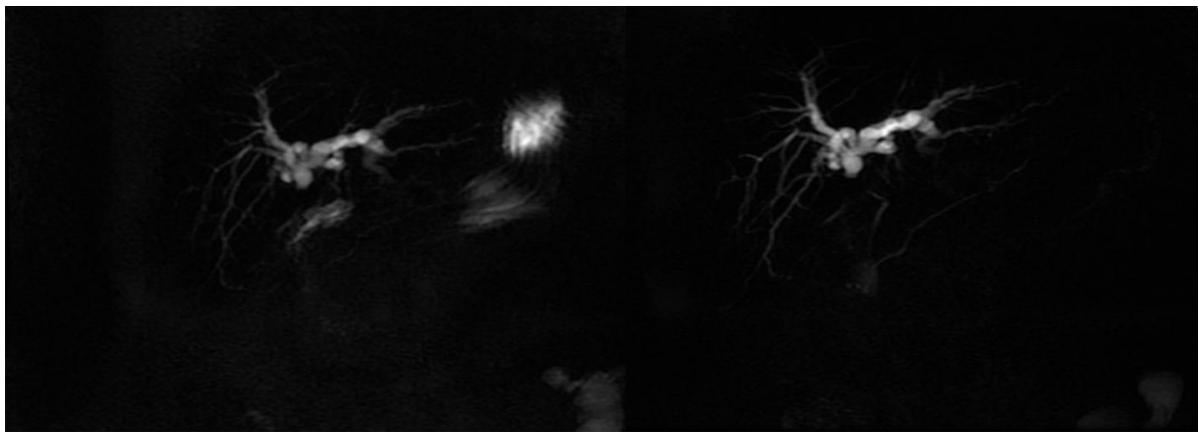
Figure 2a and b: MRCP images showing normal pancreaticobiliary ducts with a pancreas divisum (a normal variant) with pre-oral-gadolinium (2a) and post-oral-gadolinium (2b).



**Fig. 3a**

**Fig. 3b**

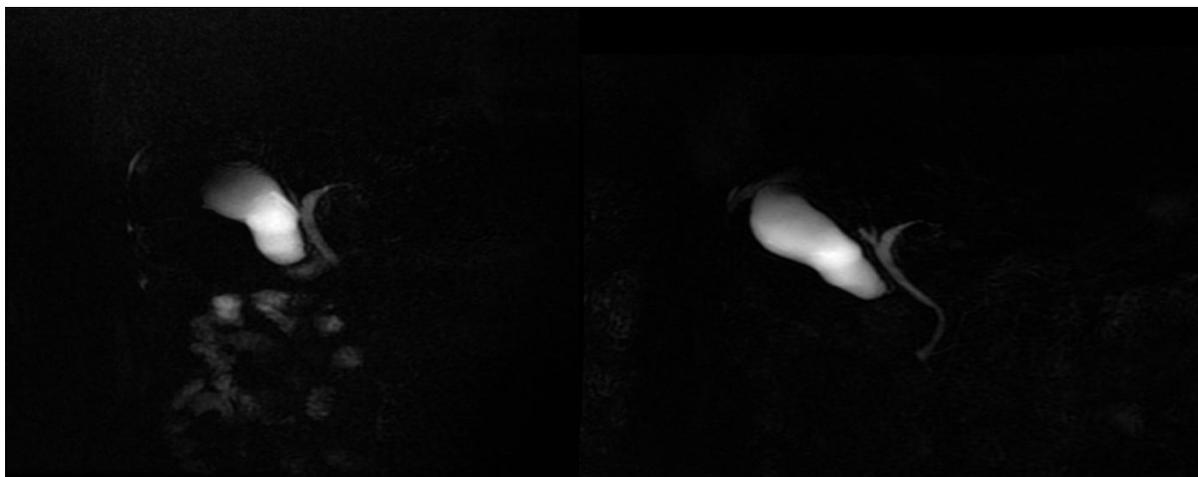
**Figure 3a and b:** MRCP images showing dilated pancreatic duct with multiple intraductal calculi with pre-oral-gadolinium (3a) and post-oral-gadolinium (3b).



**Fig. 4a**

**Fig. 4b**

**Figure 4a and b:** MRCP images showing dilated proximal common bile duct in a post-cholecystectomy patient with CBD stricture with pre-oral-gadolinium (4a) and post-oral-gadolinium (4b).



**Fig. 5a**

**Fig. 5b**

**Figure 5a and b:** MRCP images showing normal pancreaticobiliary ducts with spasm of sphincter of Oddi causing prominence of entire common bile duct with pre-oral-gadolinium (5a) and post-oral-gadolinium (5b).

Six positive cases were found in which distal CBD stricture (Fig. 4) was not seen before ingestion of oral contrast and the CBD stricture came to our notice after ingestion of the negative oral contrast in the same patients.

Eight cases showed multiple gall bladder calculi with normal common bile duct. Even the normal common bile duct was better appreciated on post-oral contrast study, as distal CBD was covered by fluid-filled duodenum and stomach.

## DISCUSSION

Our study elucidated that the consumption of 1ml of Gd- DOTA orally allowed for a better evaluation of MRCP images. There was statistically significant improvement in percentage of visualisation of pancreaticobiliary tree. It also showed that there was statistically significant increase in scores for the quality of images. In several cases, it eliminated the signal of the stomach and duodenum, either partially or completely. Thus, this aided in visualisation of the pancreaticobiliary tree structures and the main pancreatic duct.

The liquids located in the stomach and in the duodenum may overlap the hepatobiliary tree and pancreatic ductal system and pose hindrance in their visualisation in MRCP images. To prevent this problem, patients undergoing the MRCP exam are asked to fast for approximately 12 hours before the scan, and a negative oral contrast agent is administered before the exam. [10-12] Making the patient fast for 12 hours only delays the diagnosis and in turn also delays the treatment. Hence ingestion of an oral contrast prior to scan was considered. It not only aided the radiologists to come to a diagnosis quickly but also enabled early treatment. In our study, we were not only able to diagnose pathologies like distal CBD stricture, chronic calcific pancreatitis with pancreatic duct calculi and

choledocholithiasis after ingestion of oral gadolinium but were also able to initiate a timely treatment and pain relief in these patients.

Several studies in the past have used both artificial and natural (blue berry juice) exogenous agents as contrast agents. These are administered orally to allow for a better visualisation of bile ducts. [13] Coppens et al, [14] reported that the substance responsible for the signal alteration caused by contrast agents was manganese.

Chelated Gd-DOTA was chosen as the oral contrast in this study because of its established safety [15] and documented in several MR studies of gastric motility and emptying, [16,17] intestinal and colonic transit time assessment, [18] three-dimensional MR gastrography [19] and fecal tagging in MR colonography. [20] Gd-DOTA half-life of dissociation in a highly acidic hydrochloric solution (pH=1) has been measured as more than 1 month, whereas other common Gd<sup>3+</sup> chelated complexes [i.e., Gd-DTPA-BMA (Gadodiamide, Omniscan; Nycomed-Amersham, Oslo, Norway), Gd-DTPA (gadolinium-diethylenetriamine pentacetic acid-dimeglumine, Magnevist; Schering, Berlin, Germany) and Gd-HPDO3A (Gadoteridol, ProHance; Bracco, Milan, Italy)] have showed respective half-lives of dissociation of 30 s, 10 min and 3 h in the same solution. [21] The molecular framework of the meglumine ligand in Gd-DOTA contrast agent showed the maximum stability for transmetallation with other metallic ions, like Calcium, Zinc and Copper divalent cations. [15, 21, 22] However orally given Gd-DTPA has shown no adverse reactions [23] and that one study showed that 99.2% of orally administered Gd-DTPA was not absorbed and was excreted in feces. [24]

The patients tolerated the oral Gd-DOTA well. Few patients, who found on Gd-DOTA less palatable, had a sip of water following ingestion of oral contrast. Water

was not used in more than 1:15 dilution. A previous study had shown that using water in more than 1:15 dilution interfere with proper visualisation of the pancreaticobiliary tree. [23]

This study showed a remarkable increase in image visualization scores after the intake of oral Gd-DOTA. The remarkable difference in scores was elucidated by radiological interpretation. The difference in scoring (pre and post contrast) obtained by the ducts were arrayed in an increasing order as – intrahepatic duct, common hepatic duct, cystic duct, common bile duct, distal – common bile duct, main pancreatic duct. It should be noted that the ducts that presented the maximum rates of increase in scores of visualisation after the ingestion of the negative oral contrast agent have small and almost identical calibers. The ducts that posed the greatest difficulty in visualization while interpreting the MRCP images without contrast were usually these ducts that presented with highest differences in scores after intake of contrast. This was most evidently seen in case of main pancreatic duct which had the maximum score difference, followed by common bile duct - distal portion. The values found were congruent with what was expected considering the modifications the contrast agent makes in the images. This may be explained by a phenomenon that reflects the increase in the total participation of the signal from the ducts in the formation of the image of that slice after the ingestion of the negative oral contrast i.e. gadolinium chelate. It should not be considered as only a highlight of the ducts because the signal/noise relation of the pancreaticobiliary ducts does not increase significantly after the administration of the oral gadolinium. This relative signal hyperintensity is due to the pre-amplification of the signal, which results in

the compression of the dynamic range or scaling effect. [25]

## CONCLUSION

We would like to conclude that MRCP along with Gd-DOTA as a negative contrast aided in prompt and accurate diagnosis of pancreatobiliary conditions thus allowing early initiation of treatment. And that 1 ml of the gadolinium chelate proves to be a safe, economical and easily available contrast agent.

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