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Pineapple juice as a negative oral contrast agent in magnetic resonance cholangiopancreatography: a preliminary evaluation

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Abstract. The quality of magnetic resonance cholangiopancreatography (MRCP) images is frequently degraded by high signal from the gastrointestinal tract. The aim of this study is to evaluate pineapple juice (PJ) as an oral negative contrast agent in MRCP. Preliminary *in vitro* evaluation demonstrated that PJ shortened T_2 relaxation time and hence decreased T_2 signal intensity on a standard MRCP sequence to a similar degree to a commercially available negative contrast agent (ferumoxsil). Electrothermal atomic absorption spectrometry assay demonstrated a high manganese concentration in PJ of 2.76 mg dl^{-1}, which is likely to be responsible for its T_2 imaging properties. MRCP was subsequently performed in 10 healthy volunteers, before and at 15 min and 30 min following ingestion of 400 ml of PJ. Images were assessed blindly by two Consultant Radiologists using a standard grading technique based on contrast effect (degree of suppression of bowel signal), and image effect (diagnostic quality). There were statistically significant improvements in contrast and image effect between pre and post PJ images. There was particularly significant improvement in visualization of the pancreatic duct, but no significant difference between 15 min and 30 min post PJ images. Visualization of the ampulla, common bile duct, common hepatic and central intrahepatic ducts were also significantly improved at 15 min following PJ. Our results demonstrate that PJ, may be used as an alternative to commercially available negative oral contrast agent in MRCP.

Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging technique that allows evaluation of the pancreaticobiliary system. It uses heavily T_2 weighted (T2W) sequences to take advantage of the inherent contrast effect of bile.

Overlap between high signals from the pancreaticobiliary system and from the gastrointestinal tract (GIT) (stomach, duodenum and proximal intestine), is a recognized limitation of MRCP [1] and may mimic pathology [2]. The impact of high signal from the GIT is particularly problematic when single thick slice images are obtained without a thin multislice data set. Elimination of the high signal from the bowel is therefore important. This problem may in part be overcome by multiple acquisitions of the same sequence in multiple planes, or alternatively by using a negative oral contrast agent to shorten the T_2 relaxation time, and hence reduce the T_2 signal, of the fluid in the bowel. Several studies have shown that the administration of a negative oral contrast material, before performing a MRCP will improve image quality and provide good visualization of the bile and pancreatic ducts without superimposed high signal from the GIT [3–7].

A number of negative oral contrast agents are available for MR imaging of the abdomen and pelvis. Examples include Gadopentate dimeglumine, ferric ammonium citate, manganese chloride, Kaolinate, antacid, barium sulphate and ferric particles. Many of these are relatively unpalatable, become too diluted in the GIT or are expensive. Other naturally available agents have been employed. Blueberry juice is a naturally occurring inexpensive drink, that at appropriate concentrations has been shown to be an effective, well tolerated negative oral contrast agent for suppressing the signal from stomach and duodenum on T2W imaging in MRCP [8, 9]. Blueberry juice reduces the intraluminal signal of the GIT on T2W imaging, due to the paramagnetic properties of its relatively high manganese content reducing the T_2 (and T_1) recovery times. Therefore it may act as an effective negative contrast agent on T2W imaging (and a positive oral contrast agent on T1W imaging) [9].

Blueberry juice in its pure form is currently of limited commercial availability in the UK. Pineapple juice (PJ) has been proposed as an alternative naturally occurring agent that has desirable effects as an oral contrast agent for abdominal MR imaging in patients with inflammatory bowel disease [10, 11].

The aim of this study is to evaluate PJ as a potential oral negative contrast agent for use in MRCP imaging by: (a) assessment of its *in vitro* affect on T_2 (and T_1) relaxation times and relative signal intensities in comparison with other potential oral contrast agents (in the form of commercially available beverages and ''standard'' radiological contrast agents) on standard T_2 (and T_1) and MRCP sequences; (b) evaluation of its manganese concentration; and (c) evaluation of its efficacy in improving the quality of MRCP images *in vivo*.

Methods and materials

In vitro measurements

MR imaging of phantoms comprising cylinders of 150 ml of 12 different ''contrast'' agents (Figure 1) was performed

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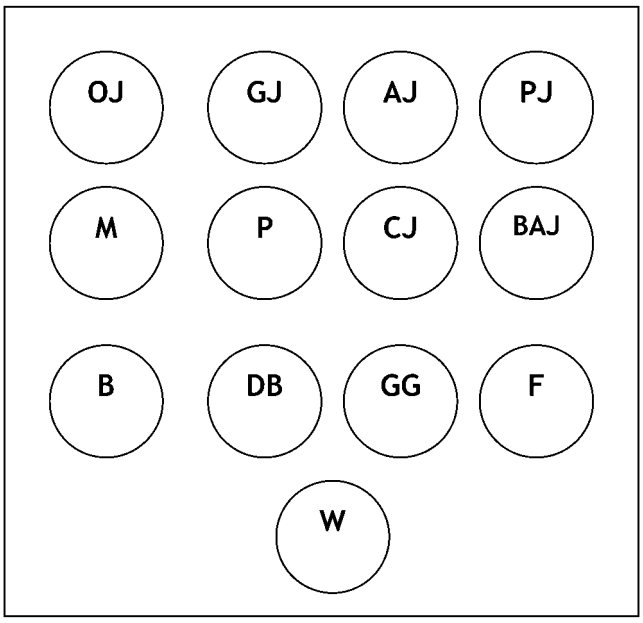

Figure 1. "Contrast agents" – orange juice (OJ), grapefruit juice (GJ), apple juice (AJ), pineapple juice (PJ), milk (M), prune juice (P), cranberry juice (CJ), blueberry and apple juice (BAJ), barium EZ Cat 2% w/v (B), dilute barium (50:50 with water) (DB), concentrated gastrografin (GG), ferumoxsil (F) and water (W).

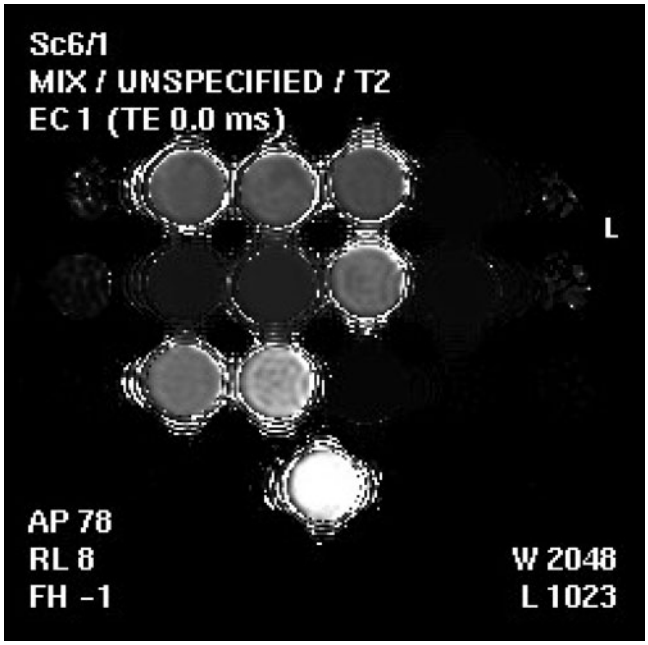

Figure 2. 2D MIXED Mode Sequence. Consisting of a multiple–echo spin echo sequence interleaved with a multiecho inversion recovery sequence, to provide single slice images [12].

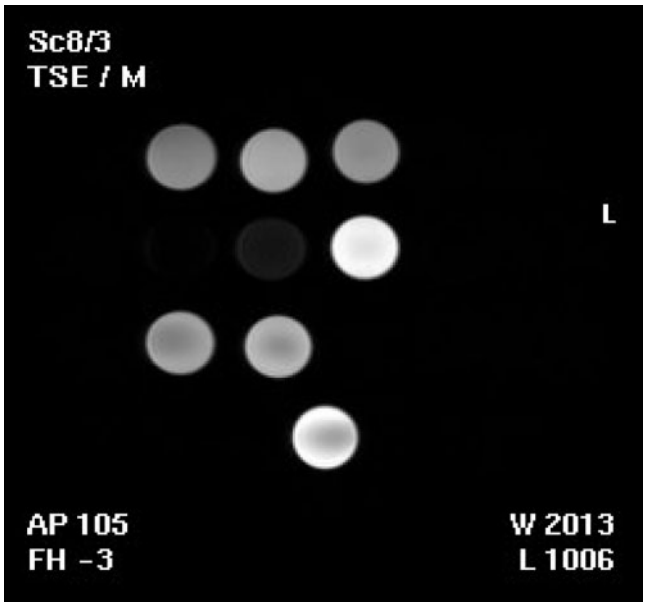

Figure 3. Single shot magnetic resonance cholangiopancreatography radial sequence (TR 8000 ms; TE 800 ms; flip angle 90°; echo spacing 7.8 ms; 5 radial sections of 40 mm thickness obtained at 12 degrees of rotation).

on a 1.5 Tesla Superconducting MR unit (Intera Gyro Scan; Philips Medical Systems, The Netherlands), with a maximum gradient strength of 30 mT m^{-1}, slew rate 75 T m^{-1} ms^{-1}, and using a Synergy Body transmit/receive coil.

The agents used were (Figure 1); PJ; a variety of commercially available beverages which include orange juice (OJ), grapefruit juice (GJ), apple juice (AJ), milk (M), prune juice (P), cranberry juice (CJ), blueberry and apple juice (BAJ); standard radiological contrast agents, that is barium EZ Cat 2% w/v (B), dilute barium (50:50 with water, DB), concentrated gastrografin (GG), ferumoxsil (F); and water (W) as control. Ferumoxsil (Lumirem®; Guerbet, Milton Keynes, UK) is a commercially available negative oral contrast, containing a colloid suspension of iron oxide particles coated with siloxane, which has superparamagnetic properties.

2D MIXED Mode (Figure 2), T_2 weighted turbo spin echo (T2W TSE), T_1 weighted turbo spin echo (T1W TSE) and single shot MRCP radial (SSH MRCP Rad) (Figure 3) were performed through the samples.

The spin–spin (T_2) and spin–lattice (T_1) relaxation times were evaluated directly from the single slice 2D MIXED mode sequence which consists of a multiple-echo spin echo sequence interleaved with a multi-echo inversion recovery sequence [12].

The relative signal intensities (signal to noise ratios) were calculated for each phantom and in each sequence by dividing the absolute signal intensities for each image by the signal of the background noise. Noise was measured by averaging over three elliptical regions of interest within the field of view (FOV), but outside of the phantoms.

The T_2 and T_1 relaxation times and relative signal intensities were measured by placing an elliptical defined region of interest over the image on a Philips Easyvision Workstation (Philips Medical Systems, Nederland BV).

PJ manganese concentration

The manganese concentration in commercially available PJ was obtained using electrothermal atomic absorption spectrometry assay (Trace Element Laboratory, Royal Surrey County Hospital, Surrey, UK).

In vivo evaluation

MRCP was performed in 10 healthy volunteers (6 males and 4 females; mean 38.9 years; range 29–55 years), following a 6 h fast. Full informed consent was obtained. Pre-contrast images were obtained before PJ. Post-contrast images were obtained 15 min and 30 min after oral administration of 400 ml of commercially available PJ. Any adverse effect, intolerance or side effects were recorded.

A standard SSH MRCP radial sequence was used (repetition time (TR) 8000 ms; echo time (TE) 800 ms; flip angle 90°; FOV 250 mm; 5 radial coronal oblique sections at 12° rotation; slice thickness 40 mm; breath hold) on a 1.5 Tesla Superconducting MR unit (Philips Gyro Scan Intera) using a Synergy transmit/receive body coil.

The images were blindly assessed, by two Consultant Radiologists (PGC, GFM) experienced in the interpretation of MRCP. A standard quantitative scoring technique was used [1] based on (a) the contrast effect, defined as the extent to which the signals from the stomach and duodenum were eliminated and (b) the image effect, defined as the extent to which the diagnostic quality of the image (*i.e.* the conspicuity of various segments of the pancreaticobiliary tree) was improved. The segments assessed were the gallbladder (GB), ampulla (A), common bile duct (CBD), common hepatic ducts (CHD), intrahepatic ducts (IHD) and the pancreatic duct in its entirety (PD) and within the head, body and tail of the pancreas (PH, PB, PT, respectively).

The contrast effect was quantitatively assessed by grading all pre and post contrast images as one of four scores, using the following scoring system: 4=excellent, entirely no signal in the stomach or duodenum; 3=good, part of the stomach or duodenum showing high signal but not affecting reading; 2=fair, high signal intensity in part of stomach or duodenum adversely affecting reading; 1=poor, high signal intensity in part of the stomach or duodenum making reading difficult.

For the image effect the reviewers were asked to assess the conspicuity of various segments of the pancreaticobiliary tree using a 4 point grading system (0 to 3); such that 0=no visualization, 1=poor visualization, 2=moderate visualization, 3=complete visualization.

Statistical analysis was performed with SPSS statistical software (SPSS Inc., Chicago, IL), using estimated marginal means and pairwise comparisons, to determine the statistical significance of differences between the mean contrast and image effect scores for the pre, 15 min and 30 min post PJ images. (A $p<0.05$ was considered as the threshold for statistical significance).

Results

In vitro study

Relative signal intensities (signal to noise ratio)

On the T2W TSE sequence (Figure 4), PJ had the lowest relative signal intensity compared with other fruit juices, milk, barium and gastrografin. However PJ had a higher relative signal intensity than ferumoxsil. Conversely on the T1W TSE (Figure 5), PJ had the highest relative signal intensity. In images obtained with the single shot MRCP radial sequence (Figure 6), PJ had the lowest signal intensity, apart from ferumoxsil and gastrografin.

Spin–lattice (T_1) and spin–spin (T_2) relaxation times

PJ had the lowest T_1 relaxation time compared with the other contrast agents and fruit juices. The T_2 relaxation time of PJ was the lowest in the group apart from ferumoxsil (31 versus 7.3, respectively) (Figure 7).

Manganese concentration

The manganese concentration in PJ was calculated at 2.76 mg dl^{-1} (502 596 nmol l^{-1}).

In vivo results

Tolerance and safety

All subjects found the PJ palatable and consumed the entire 400 ml dose. None of the subjects reported any adverse effects.

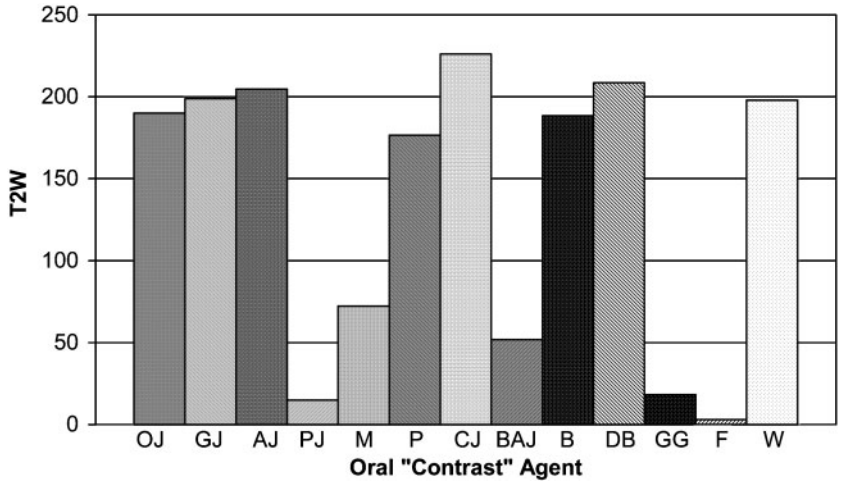

Figure 4. Graph of T_2 weighted (T2W) relative signal intensities/signal to noise ratio (SNR) of oral contrast agents. Orange juice (OJ), grapefruit juice (GJ), apple juice (AJ), pineapple juice (PJ), milk (M), prune juice (P), cranberry juice (CJ), blueberry and apple juice (BAJ), barium EZ Cat 2% w/v (B), dilute barium (50:50 with water) (DB), concentrated gastrografin (GG), ferumoxsil (F) and water (W).

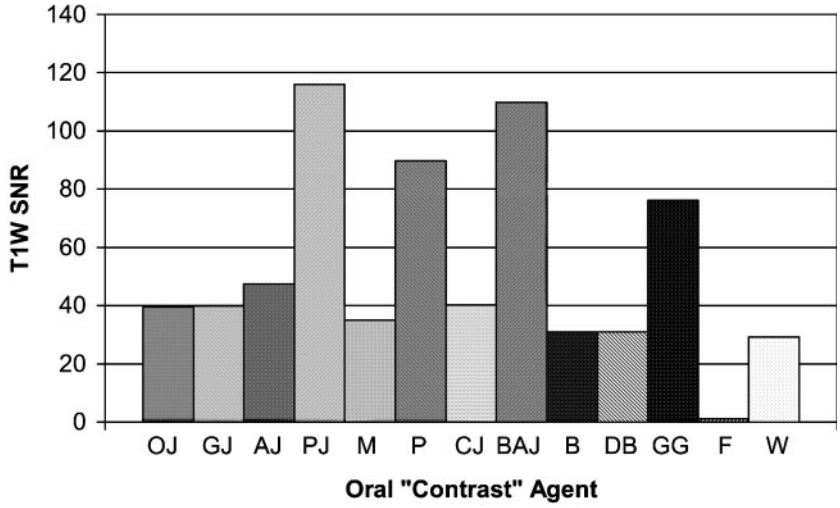

Figure 5. Graph of T_1 weighted (T1W) relative signal intensities/signal to noise ratio (SNR) of oral contrast agents. Orange juice (OJ), grapefruit juice (GJ), apple juice (AJ), pineapple juice (PJ), milk (M), prune juice (P), cranberry juice (CJ), blueberry and apple juice (BAJ), barium EZ Cat 2% w/v (B), dilute barium (50:50 with water) (DB), concentrated gastrografin (GG), ferumoxsil (F) and water (W).

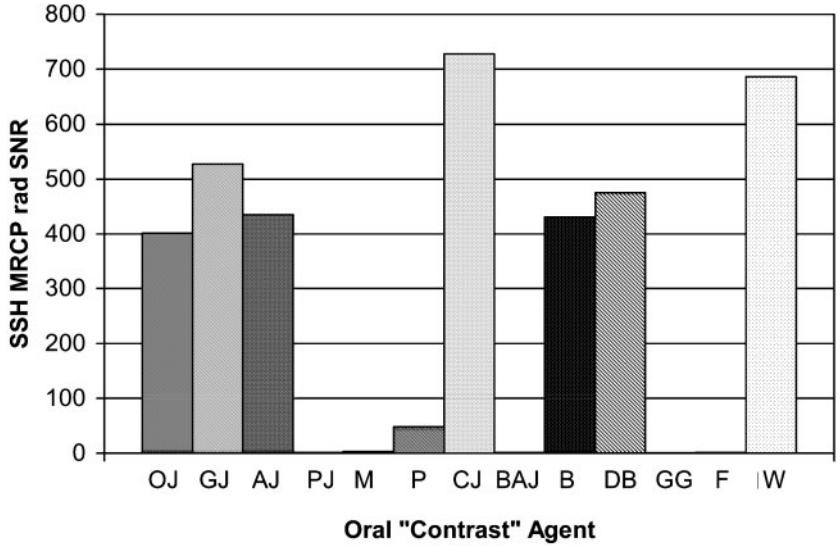

Figure 6. Graph of single shot magnetic resonance cholangiopancreatography (SSH MRCP) radial relative signal intensities/signal to noise ratio (SNR) of oral contrast agents. Orange juice (OJ), grapefruit juice (GJ), apple juice (AJ), pineapple juice (PJ), milk (M), prune juice (P), cranberry juice (CJ), blueberry and apple juice (BAJ), barium EZ Cat 2% w/v (B), dilute barium (50:50 with water) (DB), concentrated gastrografin (GG), ferumoxsil (F) and water (W).

Contrast and image effect score

Contrast effect: There was a significant improvement in the contrast effect scores (Figure 8) between the pre PJ and 15 min post PJ images ($p<0.001$), and between the pre PJ and 30 min post PJ images ($p<0.001$). There was however no significant difference in the contrast effect between the 15 min and 30 min post PJ images ($p=0.872$).

Image effect: There was a significant improvement in the image effect score (Figure 9 and Table 1) between the pre and 15 min post PJ images for visualization of the Ampulla, CBD, CHD and IHD, but no significant difference seen between the pre and 30 min post PJ images for these segments (Figure 10).

Although there is significant improvement in conspicuity of the IHD between pre and 15 min post PJ images, visualization was at best "poor". The image effect score for visualization of the pancreatic duct in total and in parts was significantly improved between the pre PJ and both the 15 min and 30 min post PJ images ($p=0.005$ and $p=0.001$, respectively). The image effect score of the GB was "moderate" to "complete", irrespective of PJ. There was no significant improvement in the image effect score for the GB visualization following PJ.

Discussion

MRCP is a non-invasive MR technique introduced in 1991 that allows evaluation of the pancreaticobiliary system. This examination has continued to evolve and it

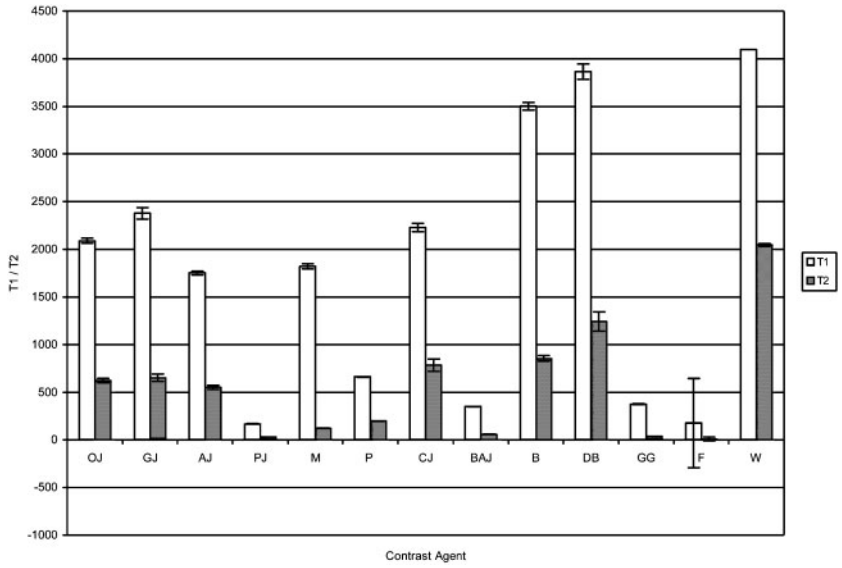

Figure 7. T_1/T_2 relaxation times. Orange juice (OJ), grapefruit juice (GJ), apple juice (AJ), pineapple juice (PJ), milk (M), prune juice (P), cranberry juice (CJ), blueberry and apple juice (BAJ), barium EZ Cat 2% w/v (B), dilute barium (50:50 with water) (DB), concentrated gastrografin (GG), ferumoxsil (F) and water (W).

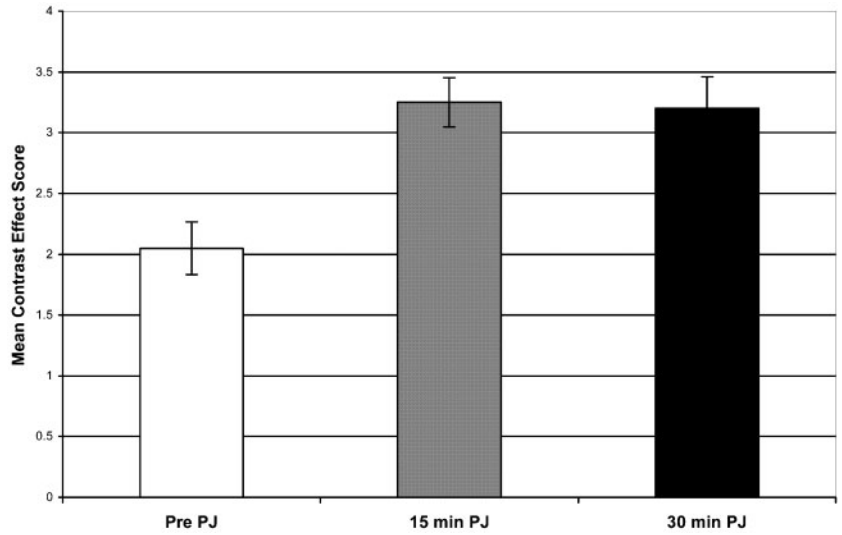

Figure 8. Comparison of mean contrast effect scores (with standard errors) between pre and post (15 min and 30 min) pineapple juice (PJ) images.

is now assuming a larger role as a rapid, accurate and non-invasive alternative to diagnostic endoscopic retrograde pancreatography (ERCP). Images are obtained without requiring instrumentation, ionizing radiation, special patient preparation, sedation or intravenous contrast material administration. It allows images of the pancreaticobiliary tree to be obtained that are similar to those from ERCP, but the non-invasive acquisition avoids the morbidity associated with complications of diagnostic ERCP (overall complications 5–10%, pancreatitis 5%, haemorrhage 1–2%, perforation<1% [13] and cholangitis 1.9% [14]). MRCP may be performed with a variety of heavily T_2 weighted sequences to depict the biliary tract, pancreatic duct and gall bladder as high signal intensity owing to the fluid within them serving as an intrinsic contrast medium.

Technical improvements, such as fast imaging sequences, have allowed imaging of the entire pancreaticobiliary ductal system using respiratory gating or single breath hold techniques with subsequent improvement in the quality of MRCPs. The accuracy of MRCP is comparable with ERCP [15–17] in the evaluation of choledocholithiasis, malignant obstruction, chronic pancreatitis and anatomical variants [2]. MRCP may reveal abnormalities or segments of the pancreatic duct not visualized on ERCP [18].

Current techniques allow for the depiction of obstructed or dilated bile and pancreatic ducts as well as normal calibre biliary systems, although the latter may be more difficult to visualize. For example, the normal pancreatic duct is said to be visualized with 94% sensitivity [19].

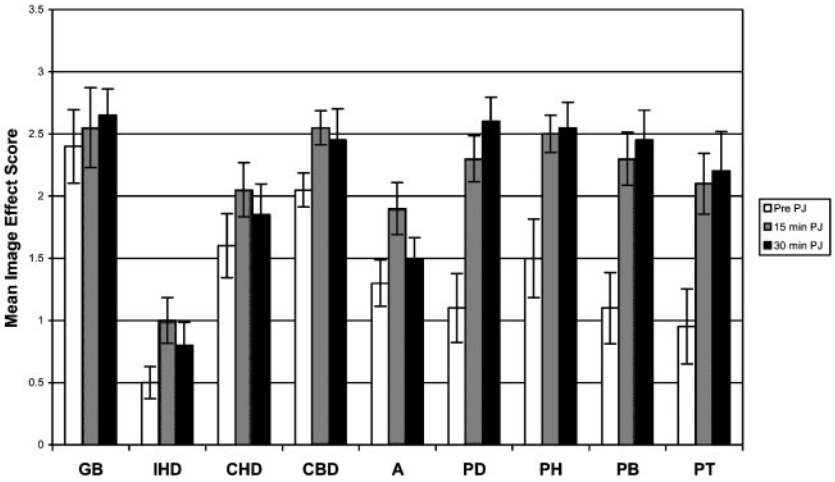

Figure 9. Comparison of mean image effect scores (with standard errors) between pre and post (15 min and 30 min) pineapple juice (PJ) images. Gall bladder (GB), intrahepatic ducts (IHD), common hepatic ducts (CHD), common bile duct (CBD), ampulla (A), pancreatic duct (in its entirety) (PD), pancreatic head duct (PH), pancreatic body duct (PB), pancreatic tail duct (PT).

Table 1. Significance (p) values for the comparison of image effect scores between pre and post PJ images for various segments of the pancreaticobiliary tree

	Segment of pancreaticobiliary system								
	GB	IHD	CHD	CBD	A	PD	PH	PB	PT
Pre *vs* 15 min PJ	0.279	0.008	0.041	0.004	0.044	0.005	0.032	0.006	0.003
Pre *vs* 30 min PJ	0.096	0.051	0.138	0.087	0.399	0.001	0.01	0.002	0.002
15 min *vs* 30 min PJ	0.443	0.104	0.223	0.619	0.022	0.051	0.78	0.394	0.555

GB, gall bladder; IHD, intrahepatic ducts; CHD, common hepatic ducts; CBD, common bile duct; A, ampulla; PD, pancreatic duct (in its entirety); PH, pancreatic head duct; PB, pancreatic body duct; PT, pancreatic tail duct; PJ, pineapple juice.

High signal intensity from intestinal fluid may deteriorate the quality of the MRCP images because it superimposes on the biliary tract. The impact of high signal from the GIT is particularly problematic when single thick slice images are obtained without a thin multislice data set. Fasting before the MRCP is not sufficient to eliminate signals from the GIT (as confirmed in our study). This superimposition of signals is a recognized limitation of the technique, which may obscure the underlying ducts or mimic pathology. Due to the proximity of the stomach and pancreas, fluid located between gastric folds may be incorrectly interpreted as fluid within ectatic, irregular pancreatic ducts as seen in chronic pancreatitis. Likewise, the duodenal bulb which contains fluid and debris is easily mistaken for the gall bladder containing calculi [2]. These pitfalls can in part be overcome by an awareness of the normal coronal anatomy of the abdomen, using multiple slice planes or suppression of the high signal in the GIT by using a negative oral contrast agent to shorten T_2 relaxation time and therefore reduce the T_2 signal of the fluid in the GIT.

It should be noted that although the use of negative oral contrast agents is beneficial in suppressing the signal in the bowel, there are potential drawbacks. Visualization of the entry point of the CBD and main pancreatic duct into the duodenum may be limited [20]. There is a single report of an oral negative contrast agent (FerriSeltz; Otsuka Pharmaceutical, Tokushima, Japan) causing loss of signal from the CBD on MRCP. This occurred in a patient following endoscopic sphincterotomy and was presumably due to insufficiency of the papilla of Vater allowing regurgitation of oral contrast agent into the CBD [20].

A number of negative oral contrast agents are available for MR imaging of the abdomen and pelvis. The ideal contrast agent is one that decreases T_2 time and gives homogeneous signal suppression, but also is safe, cheap, well tolerated, palatable and readily available. Several studies have shown the administration of negative oral contrast material before performing MRCP to provide non-superimposed visualization of bile and pancreatic ducts to improve image quality of MRCP [1, 3–7].

Oral magnetic particles have been used in MRCP as a negative contrast agent with good results [21]. However these agents have a high cost, are not widely available and are not palatable. Ferumoxsil (Lumirem) is a superparamagnetic iron oxide, consisting of a colloid suspension of iron oxide particles coated with siloxane with a magnetite core. In the presence of a magnetic field, ferumoxsil induces local microscopic magnetic fields resulting in field inhomogeneities. These induce spin dephasing, which shortens the T_2 relaxation time. This results in signal loss and consequently a dark image. Ferumoxsil therefore obliterates the fluid in the GIT by giving them a low intensity signal regardless of the sequence weighting.

Blueberry juice, a naturally occurring agent has been shown to be a well tolerated and effective oral negative contrast agent in MRCP [8, 9]. The T_2 relaxation

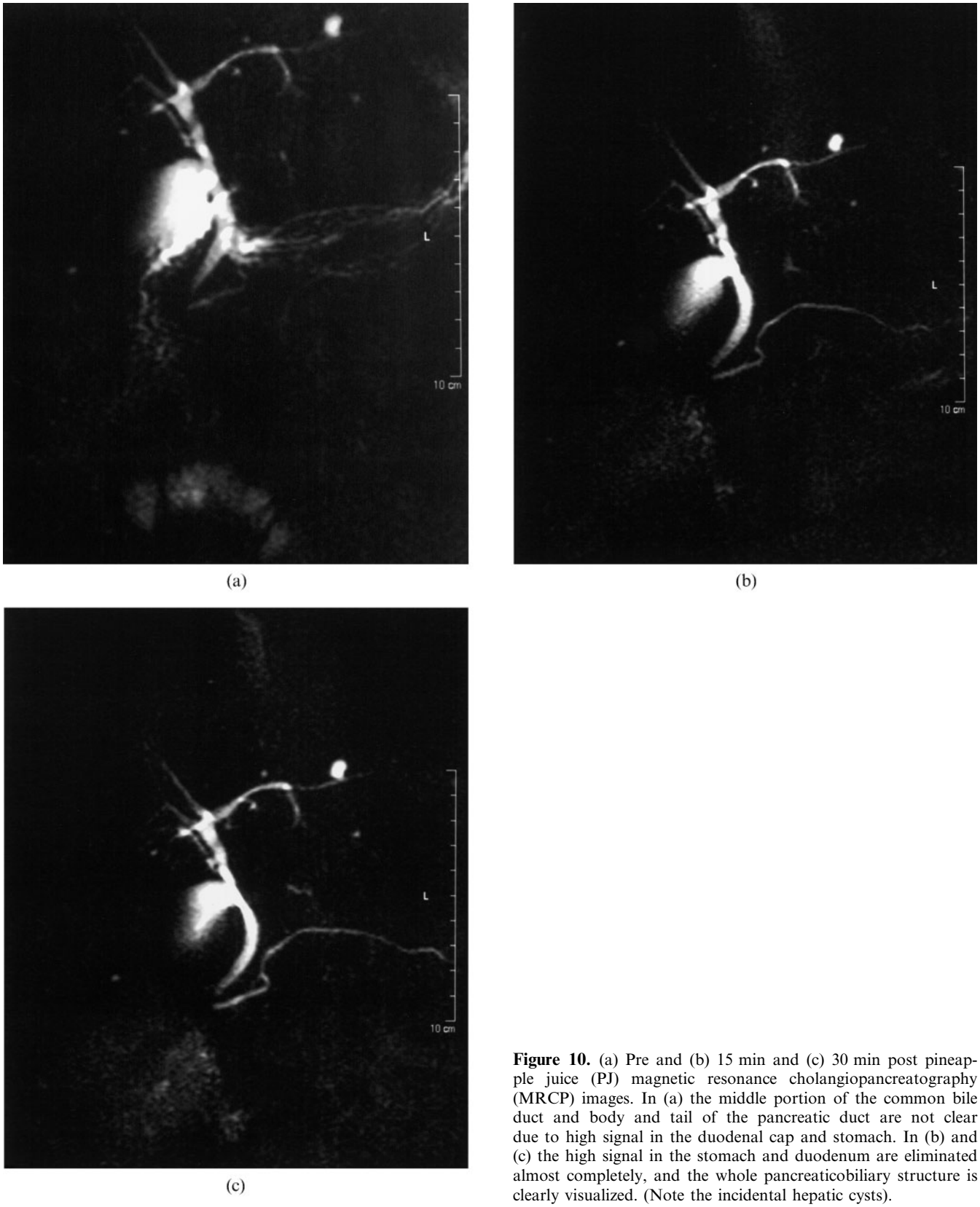

Figure 10. (a) Pre and (b) 15 min and (c) 30 min post pineapple juice (PJ) magnetic resonance cholangiopancreatography (MRCP) images. In (a) the middle portion of the common bile duct and body and tail of the pancreatic duct are not clear due to high signal in the duodenal cap and stomach. In (b) and (c) the high signal in the stomach and duodenum are eliminated almost completely, and the whole pancreaticobiliary structure is clearly visualized. (Note the incidental hepatic cysts).

enhancement of blueberry juice is due to the paramagnetic affect of the manganese within it. Unfortunately pure blueberry juice is not readily or widely available in the UK.

PJ has been proposed as an alternative naturally occurring manganese containing agent that has desirable effects as an oral contrast agent for abdominal MR imaging in patients with inflammatory bowel disease [10, 11]. In these studies PJ has been used as a positive contrast agent.

Our study demonstrates that PJ may be used as a negative oral contrast agent that significantly improves the

quality of MRCP imaging (Figure 10). Visualization of the pancreatic duct, in whole and part, is significantly improved following PJ if imaged at 15 min or 30 min post-ingestion. There is also significant improvement in visualization of the ampulla, CBD, IHD and CHD at 15 min following PJ. These findings suggest that the optimal time for MRCP imaging is 15 min following ingestion of 400 ml of PJ. The administration of PJ does not however improve visualization of the GB, although this was generally visualized adequately with or without PJ.

The negative contrast effect of PJ is due to shortening of the T_2 relaxation time resulting in reduced signal intensity from fluid in the GIT on heavily T_2 weighted imaging. This effect is likely to be due to the paramagnetic effect of the relatively high concentration of manganese in PJ (2.76 mg dl^{-1}). In a previous study the manganese concentration in commercially available PJ was calculated as 1.27 mg dl^{-1} [10].

Hirashi et al [9] reported that blueberry juice containing a manganese concentration of 3.0 mg dl^{-1} was optimal for its action as a negative contrast agent. However Papanikolaou et al [8] demonstrated that efficient GIT signal elimination was achieved with only a 1.9 mg dl^{-1} manganese concentration. This difference is presumably explained by the fact that these authors employed a very long TE sequence ranging from 1000 ms to 1300 ms to achieve heavily T2W contrast whereas Hirashi et al used sequences with a TE of 70 ms. The concentration of manganese in our study was 2.76 mg dl^{-1} using T_2 sequences with a TE of 800 ms. This demonstrated good contrast and image effect with good signal suppression from the GIT, consistent with the findings with blueberry juice [8, 9].

There are no reports of toxicity or drug interactions to PJ in the literature. Although side effects were not anticipated, this study confirmed the absence of any adverse effects. Previous evaluation of blueberry juice did not demonstrate any significant absorption of manganese into the circulation following ingestion [9, 22]. Indeed, the study by Hirashi et al [9] demonstrated no absorption of manganese into the circulation following a total dose of 18 mg of manganese in blueberry juice. This is a larger total dose of manganese than that used in our study (11.04 mg). It therefore seems reasonable to assume that no increase in manganese concentration in the circulation would occur following PJ ingestion.

Conclusion

This preliminary study demonstrates that PJ may be used as a negative oral contrast agent to improve the quality of MRCP images, using a simple technique. It is of particular benefit in improving the conspicuity of the pancreatic duct, and also improving the visualization of the common bile duct, ampulla, intrahepatic and common hepatic ducts on MRCP images.

This effect is likely to be due to the paramagnetic effect of the relatively high manganese content of PJ, decreasing the T_2 relaxation time of the fluid in the stomach and duodenum. Thus PJ has a similar profile to blueberry juice. But as well as being naturally occurring, safe and cheap it has the additional advantage of being much more readily available in the UK.

We propose that PJ can therefore be used as an alternative to commercially available negative oral contrast agents. A further study to evaluate this agent in the clinical situation is planned.

Acknowledgments

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