Author's response to reviews

Title: Three-dimensional Drip Infusion CT Cholangiography in patients with suspected obstructive biliary disease: A retrospective analysis on adverse reaction to contrast material and feasibility.

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Author's response to reviews: see over
Reviewer: A-Hon MD.PhD Kwon

General Comments
1. The authors say that DIC-CT with an infusion rate of iotroxate governed by the bilirubin value is a feasible and safe tool in patients with and without impaired biliary excretion. However, their discussion is extremely poor and insufficient.

The introduction and a majority of the discussion have been rewritten.

2. Authors say that biliary excretion might be improved by infusing the contrast media at an infusion rate governed by the bilirubin levels and the contrast media concentration will not exceed the excretion capacity of the hepatocytes. It may be true in the case of reduced excretion by hepatocytes due to inflammation, infection or malignancy. However, the common bile duct pressure rises to 170-220 mm of water following total bile duct obstruction, at which time inhibition of bile secretion is occurred. Authors should clarify the mechanism between biliary excretion of contrast media and bile duct pressure.

The following reasoning has been added to the discussion section (end of 1§);

The lack of excretion is also valuable information. Patients without excretion are likely to have either a total occlusion of the main bile duct/choledochus or a severely impaired hepatocyte function. The bilirubin value, if not already considerably elevated, is probable to escalate in these patients. In this study the lack of excretion could be explained by the final diagnosis in all patients (Table 3).

Minor Comments
1. In the protocol for infusion rate of contrast media, they defined 4 hours infusion time for the patients with serum bilirubin levels between 41 and 99 micro-mol/l. However, In Fig. 1, there are 5 patients was injected contrast media within 200 min, although their serum bilirubin levels are over 41 micro-mol/l. These five cases have to add the cases which recommendations were not followed.

There has been a typing error in Table 1. The infusion time for the patients with serum bilirubin levels between 41 and 99 µmol/L/l should be 3 hours. The Table has been corrected.
Reviewer: Jorge Soto

General Comments
1. Although the results of the study confirm that administration of iotroxate (Biliscopin) via a drip infusion is safe, the authors do not make a compelling argument about the clinical applicability of this method. This weakness can be addressed prior to publication.

Six paragraphs regarding clinical applicability/perspective of this method have been added to the end of the discussion section.

Major Compulsory Revisions
1. Discussion. This section is weak. The authors fail to provide any clinical perspective highlighting why the results of their study are important.
   a. When do they recommend use of CT cholangiography? Mention, for example, applications in biliary anatomy delineation prior to liver transplant planning.
   b. Are there any specific indications and/or contraindications?
   c. What are the relative merits and disadvantages relative to MR cholangiography? For example, non-demonstration of the pancreatic duct is a known drawback or CT cholangiography.
   d. Of note, the 142 patients were imaged with this procedure over 7 years (20/year). This is obviously an infrequent examination with limited clinical application. Why?
      The DIC-CT exams reported in study were made at a rural hospital. The number of patients referred for ERC at this hospital was therefore small. Initially it was planned to clinically evaluate DIC-CT on a material consisting of all patients referred for ERC, but after a few patients ERC for diagnostic purposes was abandoned by the surgeons.
   e. Is the fact that most of the patients included in their series were inpatients of any significance? Prolonged infusion times are problematic/impractical for outpatient settings.
      Six paragraphs regarding clinical applicability/perspective of this method have been added to the end of the discussion section.

Minor Essential Revisions
2. Introduction, first paragraph, fifth sentence. The authors’ statement that up to 80% of bile duct stones are isodense to bile and potentially not visible on CT is inaccurate and supported by a paper written in the 1960’s, before CT was even developed. Recent papers that have evaluated the performance of CT without cholangiographic contrast material obtained better results
      The first part of introduction has been completely revised. Reference list has been considerably revised and updated.

3. Materials and Methods, Administration of contrast material. How much saline solution was used to dilute the contrast material?
      The method section has been updated with the amount of saline (500 ml).

Discretionary Revisions (which the author can choose to ignore)
Materials and Methods, Evaluation of contrast material excretion.
1. Why did the authors not measure attenuation of bile in all patients with normal bilirubin levels?
The amount of work to restore the examinations from the storage media for re-evaluation was considerable. The eventual benefits of adding another 61 measurements to the 48 measurements on individuals with bilirubin <19 already made was considered to be negible.
Reviewer: Kunihiko Izuishi

General
1. There are several results that are included in the discussion section. It would be more appropriate to explain these in the results section of the paper.
   In the discussion section the paragraph “Compliance to the drip infusion scheme” has been removed and the paragraph “safety” has been reduced. The results section has been updated accordingly.

   Further detailed discussion regarding DIC-CT would be useful.
   A majority of the discussion section has been rewritten.

2. The majority of cited references were published over 10 years ago. The readers want to know more recent results. As such, more recent advances in the field and references would be valuable.
   The reference list has been significantly revised and updated.

3. What is the significance of DIC-CT(CT-cholangiography)? Is DIC-CT superior to available methods such as MRCP in the case of limited contraindication and availability? Since MRCP has become widely available and few patients have contraindications, what is the advantage of the DIC-CT method? The clinical application and recent advantage of this technology need to be discussed in the discussion.
   Six paragraphs regarding clinical applicability/perspective of this method have been added to the end of the discussion section.

Minor Essential Revisions
   1. In the materials and methods, authors describe the statistical methods using SPSS. However, statistical significance is not noted in the results section. Please indicate the statistically significant differences where they occur.
      The sentence “Statistical significance was determined by simple linear regression analysis using SPSS v.12.0.1 (SPSS inc. Chicago, IL, USA)” has been omitted.