Author's response to reviews

Title: Management of patients with biliary sphincter of Oddi disorder without sphincter of Oddi manometry

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Author's response to reviews:

Dear editor,

Thank you for giving us the opportunity of submitting a revised version of our paper entitled "Management of patients with biliary sphincter of Oddi disorder without sphincter of Oddi manometry". We would like to thank the reviewers for a thorough review of our paper. We feel that by following their suggestions we have improved the paper considerably. Changes are highlighted in the revised version of the paper. Our point-to-point response to the comments of the reviewers are as follows:

Reviewer 1 (Benedetto Mangiavillano)

Major comments

1. No prophylaxis with anti-proteaseic drugs was given. This information has been added to the Methods ("Follow-up and data collection" section) of the revised version of the manuscript (p. 6).

2. A flow chart for the management of patients with a clinical diagnosis of biliary SOD has been added in the Methods of the revised version of the manuscript (figure 1).

3. Results are summarized in table 2 that has been added in the Results in the revised version of the paper.

4. A new table on patients undergoing endoscopic sphincterotomy (table 3) has been added to the paper as suggested by the reviewer. Risk factors for post-ERCP pancreatitis (female gender, pre-cut technique, etc), no of ERCPs, and outcome data are summarized in the table. The section of the Results "ERCP and sphincterotomy" was partly re-written as a result of the addition of the table. None of the patients had had previous pancreatitis. No patient in the current study had gallbladder or biliary stones or sludge on imaging or ERCP and this information has been added in the Methods ("Patients" section) in the
5. Twenty-four patients underwent ERCP. As outlined in the "ERCP and sphincterotomy" section of the Results one patient was found to have non-dilated duct and did not have a sphincterotomy performed. Thus, 23 patients underwent sphincterotomy. This has been explained further in the revised version of the paper ("ERCP and sphincterotomy" section of the Results). A total of 8 patients had post-ERCP pancreatitis. Six of these pancreatitis occurred after the first ERCP-sphincterotomy (6/23, 26%). This has been added to the Results in the revised version of the paper ("ERCP-related complications" section).

6. Complications occurred in 9/50 procedures (18%). However, 7 out of 9 of these complications (i.e. 78%) occurred at the first ERCP. We have replaced the percentage (78%) with the phrase "The majority" in the abstract in order to avoid confusion. The exact percentage if, of course, still mentioned in the Results.

Minor comments

1. The phrase "... patients with biliary SOD..." was replaced by "...patients with a clinical diagnosis of SOD..." in the Management section of the Methods (p.5) as suggested by the reviewer.

2. The sentences about the potential multifactorial etiology of SOD are not included in the Abstract of the revised version of the paper.

Reviewer 2 (C Mel Wilcox)

Response to major comment

As pointed out by the reviewer the two main limitations of the study, i.e. partly retrospectively collected data and absence of quantitative measure of abdominal pain, as well as the need for future prospective interventional trials have been discussed in the paper. However, all patients were managed and response to treatment was assessed under the care of a single physician with long experience in the management of biliary disorders. This is also mentioned in the Discussion (2nd last paragraph).

We feel that data from our cohort may reflect the everyday practice and dilemmas that clinicians looking after this group of patients are faced with. We hope that our paper will stimulate further research in the area. As also pointed out in the Discussion, our data, contribute to an accumulating amount of evidence suggesting that SOM results may not necessarily define the management course in future trials.

Response to specific comments

1. The word "praxis" has been replaced by the word "practice" in the Introduction.

2. The point is well-taken. The relevant parts of the Background and Discussion on ERCP (in particular the part referring to pancreatic stenting) have been
reduced in the revised version of the paper.

3. Doses of medications have been added in the Management section of the Methods. Also all patients had had a trial of PPIs that had been ineffective. This piece of information has also been added in the Patients section of the Methods in the revised version of the manuscript.

4. Assessments were done in clinic (by the physician) and all patients were managed under the care of a single physician with experience in the management of hepatobiliary disorders. The lack of a standardized instrument is a clear limitation of the current study. Please see 2nd last paragraph of the Discussion of the paper and response to the major comment of the reviewer as well.

5. Patients were followed up until last outpatient clinic visit during the study period, until discharge or until last clinic visit before being lost to follow up (this is mentioned at the beginning of the "Follow-up and data collection" section of the Methods). Patients were not followed up after discharge and follow-up times were calculated as defined above. However, discharged patients, in the UK system, would have contacted their general practitioner in the first instance in the event of recurrence. We would have expected general practitioners to have re-referred any discharged patients with a recurrence to our institution as referral elsewhere would be geographically impractical. However, we cannot exclude that discharged patients who may have moved from the area of Oxford may have been treated elsewhere for a recurrence. This is mentioned in the limitations section of the Discussion in the revised version of the paper.

6. Reliable time data for the development of recurrence were available for 9/12 patients who developed recurrence in this study. These patients were treated with biliary sphincterotomy. Recurrence developed in a mean of 13 months (median 18 months, range 1-24 months) post-sphincterotomy. This information has been added in the Results ("ERCP and sphincterotomy" section) in the revised version of the paper.

7. Please see response to major comment as well as to specific point 4 of the reviewer.

8. A table has been added to present the results including follow-up (table 2, please also see response to major point 3 of reviewer 1). The number and proportion of patients who had previously undergone cholecystectomy (26/59, 44%) is mentioned in table 1 characterizing the cohort. The number and proportion of patients with an intact gallbladder in situ has been added in the beginning of the Results section of the revised version of the manuscript as suggested by the reviewer. Also, the fact that the presence of an intact gallbladder did not influence symptom burden at follow up has been added in the Results section as well (p.9). As mentioned in the Discussion, previous studies have shown elevated sphincter pressures in a proportion of patients with biliary pain and intact gallbladder and SOD is thought to occur in these patients. However, we did not perform radionuclide imagine for gallbladder dyskinesia in
our cohort and thus we cannot exclude that some of the patients with an intact gallbladder would have benefited from cholecystectomy. This has been added in the Discussion in the revised version of the manuscript.

9. A table with ERCP data of all patients (table 3) has been added in the revised version of the manuscript. The number of ERCPs that each patient underwent as well as the reasons for repeat procedures are given in the table and its footnote. Re-stenosis was defined as scarring at the biliary orifice post-sphincterotomy not allowing the free passage of a small balloon (10-12 ml). This has been added in the revised “ERCP and sphincterotomy” section of the Results. We agree with the reviewer that a relatively large proportion of patients had more than 1 ERCP procedures (14/59, 24%). The numbers of ERCPs reported includes procedures required for stent change, failed procedures, repeat procedures after a pre-cut sphincterotomy needed to obtain access into the common bile duct and perform over-the-wire sphincterotomy, etc. As far as biliary stenting is concerned we use a trial of stenting prior to referring patients for surgery in our practice. Although the surgical management of SOD patients is controversial, good long-term outcomes have been reported (J Am Coll Surg 2008; 206(5):908-17; Arch Surg 2005; 140 (5):504-13). In our practice we have found that some patients despite having an adequate sphincterotomy seem to benefit from biliary stenting and that surgical treatment may be beneficial in this group of patients. A paper on surgical therapy of patients with SOD in underway from our institution and thus we would not like to expand on this matter in the manuscript.

10. Pre-planned comparisons were those among patients with different SOD types, those with vs. without a dilated CBD, and those with vs. without an intact gallbladder. We did not use any statistical test to control for multiple comparisons as almost none of the statistical analyses performed yielded statistically significant results.

11. The Discussion in the revised version of the paper has been reduced by approximately 25% (excluding the sentences that have been added following response to the comments of the reviewers).

Kind regards

Evangelos Kalaitzakis MD, PhD