

November 30, 2014

Dear Editor and Reviewers,

We would like to resubmit our revised manuscript (14853-edited). We would like to thank you and the reviewer for the insightful and helpful comments. We believe these suggested changes significantly enhanced the quality of our manuscript.

Title: Prophylactic tracheal intubation for upper GI bleeding: A meta-analysis

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Name of Journal: *World Journal of Meta-analysis*

Manuscript #: 14853

The manuscript has been improved by suggestions and comments by the reviewers and editor.

Editor: Good ideas. All the changes that were suggestive have been made as follows.

- We have added the following to the title page:

“Conflicts of Interest: The authors have no conflicts of interest for this manuscript.”

“Data-sharing: No additional data are available.”

- Given that I am a biostatistician, we have placed the following statement at the end of the methods:

“Biostatistics: The corresponding author (MB) is a biostatistician and has reviewed and approved all statistical data in the manuscript. Four of the authors (AH, HH, DN, MB) are extensively trained in the statistics used in meta-analysis.”

- Figure 1 will be re-submitted as a decomposable figure.

Reviewer #1:

1.UGIB should exclude in short title

- Good idea. Is has been excluded in the short title. It reads as follows:

“Prophylactic intubation”

2.Meta-analysis should exclude in key word, complication, pneumonia and aspiration could be add.

- Good point. Meta-analysis has been excluded and complication, pneumonia, and aspiration included in key words as follows:

“Key words: Prophylactic endotracheal intubation; upper gastrointestinal bleeding; endoscopy; complication; pneumonia; aspiration

3. Figure 5 can be omit.

- Figure 5 has been omitted.

Reviewer #2:

Title: Prophylactic tracheal intubation for upper GI bleeding: A meta-analysis

This is a very early systematic review and meta-analysis investigating the impact of prophylactic tracheal intubation on iatrogenic pneumonia, all-cause mortality and aspiration arising from complications due to endoscopy for upper GI bleeding. While this is no doubt an important, and clinically relevant research question, only a small number (n=4) of studies were included and one must question the validity of pooling two retrospective studies and the findings from two conference proceedings together. However, I do not feel that this should be an impediment to the articles publication on the grounds that it may help serve to highlight that more prospective studies and RCTs in this area are needed.

The authors have undertaken a comprehensive literature search across four electronic databases (although studies were limited to the English language) and have followed MOOSE guidelines in its conduct. The quality of included studies was assessed using a quality assessment tool for quantitative studies which has been formally compared to the Cochrane risk of bias tool.

Specific Comments:

1. Abstract: UGIB – should be spelt out in full before first mention. As should ACG and AGA in the results section or alternatively include them amongst the list of abbreviations.

- Good points. The abbreviations are now spelled out and they have been added to the abbreviations section.

2. Methods: Reference to Figure1 and Table 1 should only be made in the results section. Insert (AA,MB) after ‘All studies that met the inclusion criteria were reviewed by two investigators’

- We agree. The references for Figure 1 and Table 1 have been placed in the results section and (AA,MB) have been adjusted as follows:

“All studies met the inclusion criteria were reviewed by two investigators (AA, MB).”

3. Statistical analysis – I would usually suggest the investigating sources of heterogeneity by performing subgroups on study location/time period/exclusion of abstracts but there are too few studies to do this. This could be mentioned as a limitation. Also, where formal tests for publication bias undertaken i.e.: Begg/Egger tests or was the assessment based on visual inspection. If so, please specify.

- We agree. Subgroup analysis should be performed if heterogeneity is observed. However, as you mentioned, given the number of studies in the meta-analysis is small, it is not amenable to this type of subgroup analysis. We have added a line in the limitations as follows:

“However, given the limited number of studies, subgroup analysis for sources of heterogeneity (such as location, timing, abstract exclusion) was not performed.”

- Publication bias was assessed visually by funnel plot. Given the symmetry of the plot, we did not perform the Begg-Mazumdar or Egger analysis. In cases where the funnel plot is asymmetrical, we perform further analysis such as these two equations.

4. The discussion is a little oddly structured, I would have expected to see it begin with the first outlined strength (i.e.: “this is the first meta-analysis...”) and then go on to discuss salient findings. There is also no discussion of the strengths/weaknesses (critical appraisal) of the four included studies – which is an important component of a review. The authors state ‘the results should be interpreted with caution in light of the limitations of meta-analysis’, but I think the point should be made that it is not the meta-analysis but the limited number of studies feeding into it which must be cautiously interpreted. For example, in figure 2, the study by Rehman et al is responsible for 78.6% of the pooled effect estimate, and was the only study to record a pneumonia event in the no PI group. In my opinion, the studies by Koch and Tang with their extremely high upper 95% CIs just inflate the observed association. The validity of the pooled estimate, really comes down to how reliable the estimate from the Rehman study was – this needs commentary in the discussion.

- Great points. We have added a paragraph discussing the retrospective studies, including their strengths and limitations. The first and second paragraphs of the discussion is as follows:

“In an effort to provide airway protection and reduce aspiration complications, providers may elect to perform tracheal intubation for patients presenting with UGIB. Unfortunately, there are no published guidelines to direct the use of endotracheal intubation in this group of patients, partly because of the lack of evidence-based recommendations. Emergent tracheal intubation is clearly indicated as a measure to protect airways in specific clinical presentations such as patients with altered mental status or those hemodynamically unstable. On the other hand, complications can arise directly from emergent tracheal intubations and the benefits of tracheal intubation should be weighed against the risks in each case individually. Schwartz et al found that emergency intubation results in esophageal intubation in 8%, new pulmonary infiltrates identified post-intubation in 4%, and 3% died within 30 minutes of intubations, although those who died were those hemodynamically unstable before intubation^[30]. Only few studies evaluated this important subject and all were of retrospective design and varied in results^[24-27].

Koch et al evaluated the outcomes of 69 patients with variceal bleeding who were either prophylactically intubated or not intubated prior to endoscopy and discovered significantly more aspiration in those who were prophylactically

intubated^[25]. However, no differences were noted for mortality or length of stay^[25]. Rehman et al utilized 49 matched controls to 49 patients with UGIB and shock, cirrhosis, or hematemesis^[24]. Although cardiopulmonary complications are common in this population, no difference was discovered between the prophylactic intubation versus no prophylactic intubation in matched controls for mortality, length of stay, pneumonia, or aspiration^[24]. Similarly, an abstract by Tang et al showed no significant differences between prophylactic intubation versus no prophylactic intubation for mortality, pneumonia, and hospital length of stay in 69 patients with suspected variceal hemorrhage^[27]. In contrast, an abstract by Perisetti et al demonstrated that prophylactic intubation in patients with UGIB resulted in significantly more aspiration, length of stay, and mortality during hospitalization^[26]. Therefore, results has varied among the retrospective studies in regards to important outcomes such as aspiration, pneumonia, and mortality.

Due to this variability, we conducted this meta-analysis to evaluate the available evidence from four published retrospective studies that compared outcomes in UGIB patients who were prophylactically intubated and those who were not prophylactically intubated."

- We also agree that the limited studies is the reason the data should be interpreted with caution. Therefore, we have added the line to as follows:

"Although these results must be interpreted with caution in light of the small number of studies in this meta-analysis leading to one or two studies having significant weight on the results, this study addresses the issue of prophylactic intubation prior to endoscopy in patients with UGIB."

5. Table 1 - as this review is not an analysis of RCTs (where baseline characteristics between the groups would be expected to be equal), I think it would be useful for the reader to know a bit more about the differences in baseline characteristics of the study populations under investigation i.e.: age (age-group), gender, comorbidity status, did the case-control studies use population-based controls or hospital controls etc. Where available, this information may help determine potential sources of heterogeneity and selection bias. The authors could also note individual study adjustments i.e.: Rehman *et al* matched controls on the propensity of intubation (which would mean that the differences in findings wouldn't be expected to differ by the indication/prognostic factors leading to intubation), what did the other studies do? I would remove the months from the time column and just state the years (period) in which the study was conducted. I would also suggest adding the study reference number into the reference column.

- Good points. We have added a few more columns to table 1 to show age, gender, and population base in each of the studies. We have removed the months for the time column and have added the reference numbers.

6. Figure 5 – It might be a good idea to plot the confidence limits around the SEs to aid the reader's visual assessment of asymmetry in the funnel plot.
- Based upon another reviewer's comments, figure 5 has been removed.

Reviewer 3:

A major argument for the publishing is, that it is his is a first meta-analysis on the topic of prophylactic endotracheal intubation during endoscopy for upper GI bleeding. The authors could not convincingly background their choice to perform this metaanalysis. Though authors state in the introduction, that "Although significant morbidity and mortality can result from pulmonary aspiration that may complicate endoscopy...", but this statement has no references, especially in the setting of endoscopies for upper GI bleeding. It is not surprising, that there are no prospective studies on the topic. Probably it is not so actual and important? The meta-analysis based on of retrospective studies must be evaluated with caution. Retrospective data have potential bias. Nevertheless, we have to admit, that the meta-analysis provides us available information. Some revisions could be performed:

1. In the introduction to make an accent why this problem is important in this specific setting (Upper GI bleeding).

- Great idea. We have added the following line to the introduction.

"However, controversy does exist, even at our own institution, of the utility of prophylactic intubation in patients with UGIB. The largest reason for this controversy is that only a few observational studies have been done to evaluate the utilization of tracheal intubation in the setting of UGIB^[23-27]."

2. Perhaps introduction could be shorter? Especially first part?

- We agree. We may have been too detailed in epidemiology and costs. We have adjusted the introduction as follows:

"Upper gastrointestinal bleeding (UGIB) remains an important etiology of morbidity and mortality in the United States^[1]. Health-resources utilization in those with UGIB is significantly higher than those without UGIB^[2-5]. Although UGIB hospitalizations have decreased in the last decade, likely because the use of acid suppression therapy^[6,7], mortality has not decreased and UGIB continues to be a significant cause of hospital admissions^[8-13].

Many strategies have been implemented to reduce the morbidity, mortality, and cost associated with UGIB, including scoring systems, appropriate resuscitation, and improvements in endoscopic and non-endoscopic therapies.^[14-19]. In an attempt to reduce aspiration and aspiration pneumonia in patients presenting with UGIB, it is plausible that prophylactic tracheal intubation prior to performing endoscopy, but is there any evidence to support such a practice. Tracheal intubation might prevent aspiration in selected cases but outcomes could be related to how experienced medical personnel performing the intubation is and how sick the patient is, i.e. with altered mental status or massive bleeding^[20-22]. However, controversy does exist, even at our

own institution, of the utility of prophylactic intubation in patients with UGIB. The largest reason for this controversy is that only a few observational studies have been done to evaluate the utilization of tracheal intubation in the setting of UGIB^[23-27]. These studies evaluated outcomes such as mortality, aspiration, aspiration pneumonia, and hospital length of stay. As our knowledge to answer the question of the utility of tracheal intubation in the setting of UGIB is still lacking, we conducted a meta-analysis to further evaluate such limited data."

3. Probably one of endpoints could be the success of endoscopic hemostasis?

- Good idea. Success of hemostasis was not examined in the studies and therefore not able to be included in meta-analysis. Markers for this would be need for repeat scope, need for surgery or interventional radiology assistance, or clinical parameters such as drop in hemoglobin. In the future, if more studies become available, this may be examined.

4. Conclusions: I do not believe that there is "the need for a randomized controlled trial to assess the issue of prophylactic intubation prior to endoscopy in patients with UGIB."

- We have adjusted this line as follows:

"Although these results must be interpreted with caution in light of the small number of studies in this meta-analysis leading to one or two studies having significant weight on the results, this study addresses the issue of prophylactic intubation prior to endoscopy in patients with UGIB. Based upon these results, prophylactic tracheal intubation is not beneficial in patients with UGIB and should not be recommended."

5. I would advise to make the recommendations that there are no data indicating the need of intubation?

- Good idea. We have added a line to the end of the discussion.

"Although these results must be interpreted with caution in light of the small number of studies in this meta-analysis leading to one or two studies having significant weight on the results, this study addresses the issue of prophylactic intubation prior to endoscopy in patients with UGIB. Based upon these results, prophylactic tracheal intubation is not beneficial in patients with UGIB and should not be recommended."

Reviewer 4:

Dear Author, This article should be published (Prophylactic tracheal intubation for upper GI bleeding: A meta-analysis). But, the priority is not high for publication. Because everybody knows that prophylactic tracheal intubation is not necessary before endoscopy. Sincerely yours.

- Thanks for your comments. At our institution, there has been some significant debates regarding the utility of prophylactic intubation prior to endoscopy in patients with UGIB. This meta-analysis demonstrates your point, that prophylactic intubation may not be necessary and may be harmful to patients with UGIB.

Thank you for considering our manuscript for publication in your journal.

Sincerely,

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