NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

*The corresponding author has opted to make this information publicly available.

Personal or nonessential information may be redacted at the editor’s discretion.

Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
RE: Manuscript Number ONG-18-1766

Oral riboflavin to assess ureteral patency during cystoscopy: A randomized controlled clinical trial

Dear Dr. Stitely:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the “track changes” feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 09, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This was a well designed double blind randomized control trial looking at the use of riboflavin to assess and quantify the ease of ureteral patency during cystoscopy.

Abstract: Over all this was a concise abstract with clear objectives and conclusions supported by the results.

Introduction:

Overall this a good review of the topic and rationale for the chosen use of riboflavin. The discussion of availability and potential side effects of the other agents listed is clinically relevant. The recent RCT by Grimes et al looking at multiple agents including manitol is an important study.

1. Was there any attempt at using similar questionnaires for cystoscopy? They seem to use an analog score 0-100.

Materials and methods:

2. Line 116-117 Blinding both the subjects and clinicians was very important. Does the placebo including vitamin D3, cholecalciferol, 1000 IU have any effect on general diuresis or coloration which may bias the outcomes?

3. Line 124-125 The use of blinded video was unique in comparison to other studies and helps with inter rater reliability.

4. Line 128-130 Was there any validation of this 1-3 coloring system a priori?

Secondary objectives

5. Similar to the other comments was there a validated scale used for ease of identification of ureter efflux?

6. The categorical identification between riboflavin vs. placebo was this up to the 3 min mark or was this overall regardless of whether it took longer than 3 min.?

7. Line 137-140 The power analysis was described in depth and accounted for drop out. It is not clear however if these are reasonable assumption since the survey and rating scales were not previously validated.
8. Line 169-174 The authors addressed compliance both by reminder calls as well as return of the medication label with date and time.

9. Line 195-207 This was a good explanation of the descriptive data analysis and why appropriate comparative tests were chosen. It is easy to follow.

Results

10. Table 1 Was there more information on medication or other medical problems that would alter or delay visualizing ureteral efflux such as HTN, DM, medication including diuretics EBL and intraoperative IVF? If available this should be included.

11. Table 3 This is an important description of what was found if ureteral efflux was not seen. Please clarify if the end point was strictly timed and recorded as 3 min before the outcome of non visualization was determined.

12. Figure 2 Perhaps a picture side by side of all three colors to give the reader an idea of what the differences were visually.

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13. This is a thoughtful review of the strengths and limitations of this study. The focus of using video with a separate blinded observer contributes to inter rater reliability at the same time. The authors should be commended for a meticulously designed trial.

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This is a double masked randomized control trial comparing riboflavin versus placebo for ease of ureteral patency following prolapse surgery. This well-written, straightforward trial compares a readily available, affordable over the counter medication to ease assessment of ureteral patency. The authors found through surgeon assessment and video review that riboflavin improved the ability to identify ureteral efflux. A few issues need to be addressed.

1. One issue that makes this study appealing is how cost effective riboflavin; given that indigo carmine way be available it would be helpful to have information on the cost of the other medications discussed, ie phenazopyridine, fluorescein.

2. How was compliance assessed beside patient writing the time and date they took the medication? Did 100% of patients report taking the medication as instructed?

3. Was this study registered on clinicaltrial.gov?

4. Were the other RCTs published on other medications for urinary patency used for the power analysis?

5. The authors need to add more discussion on the other RCTs that have been done on this topic

REVIEWER #3:

This manuscript describes a RCT designed to compare ureteral patency assessment after PO riboflavin versus placebo. The study idea is simple, and the execution of the study was very good. The manuscript is well written and easy to follow.

I have no questions

STATISTICAL EDITOR’S COMMENTS:

1. line 61: Should round this to 0.71.

2. lines 61-62: Study not powered to evaluate urinary tract injuries. 0/33 has 95% CI upper bound of 11%.

3. lines 141-151: There was one primary outcome (color difference, lines 47-49), if the power analysis was designed to evaluate both color difference and "ease of visualizing the ureteric jets" (of which there were two hypotheses, then a stricter alpha value should be used, since a total of 3 hypotheses are being tested. Otherwise, should report the primary as color difference and the others (ease of visualization by two metrics and confirmation of bilateral ureteral patency were each secondary outcomes.
4. Table 1: Since this was a RCT, there is no need to statistically compare the cohorts. Differences should be due to random chance.

5. In Tables of results, should clearly demarcate the stated primary from the secondary outcomes.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. This statement must appear at the end of your Materials and Methods section. The statement should include:
   1. Whether individual deidentified participant data (including data dictionaries) will be shared;
   2. What data in particular will be shared;
   3. Whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.);
   4. When the data will become available and for how long; and
   5. By what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Examples of statements can be found online at http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf.

3. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women’s Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal’s author agreement form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.
In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows:
Original Research articles, 300 words. Please provide a word count.

8. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

***

If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 09, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
27 October 2018

Dear Editorial Staff at Obstetrics and Gynaecology,

Thank you for considering our manuscript ONG-18-1766 "Oral riboflavin to assess ureteral patency during cystoscopy: A randomized controlled trial" for publication. We have reviewed and carefully considered all of the points raised by the reviewers and we have revised our manuscript accordingly.

The revised manuscript is submitted with tracked changes, and the response to the reviewer queries is pasted below. All authors are in agreement with the content of the re-submitted revised manuscript.

Revised figures and video content are included with the revision in the Editorial Manager program.

OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

Thank you for the opportunity to submit our article for publication in your journal.

REVIEWER COMMENTS:

REVIEWER #1:

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1. Was there any attempt at using similar questionnaires for cystoscopy? They seem to use an analog score 0-100.

The study by Grimes et al was published in November 2017, after we had begun enrolling subjects in our study, so our evaluation method was developed independently of the Grimes study.

Materials and methods:
2. Line 116-117 Blinding both the subjects and clinicians was very important. Does the placebo including vitamin D3, cholecalciferol, 1000 IU have any effect on general diuresis or coloration which may bias the outcomes?

We are not aware of any effect on colouration of urine or diuresis from the administration of the cholecalciferol doses administered in the study.

3. Line 124-125 The use of blinded video was unique in comparison to other studies and helps with inter rater reliability.

4. Line 128-130 Was there any validation of this 1-3 coloring system a priori?

The color scale was not validated a priori.

Secondary objectives

5. Similar to the other comments was there a validated scale used for ease of identification of ureter efflux?

The rating scales were not validated a priori.

6. The categorical identification between riboflavin vs. placebo was this up to the 3 min mark or was this overall regardless of whether it took longer than 3 min.?

This data point was not time limited. The 3-minute cut-off was a time point when the operating surgeon could administer additional agents for clinical indications. This time point was included into the study design so as to not unnecessarily prolong the surgical case solely for the purposes of the study. Of course, the timing of the ureteral jet is affected by a number of factors such as hydration status, baseline renal function, blood loss, and even the timing of placing the cystoscope. The timing of the decision to administer additional agents was much greater than three minutes in all cases when additional agents were used.

7. Line 137-140 The power analysis was described in depth and accounted for drop out. It is not clear however if these are reasonable assumption since the survey and rating scales were not previously validated.

We acknowledge this point. The assumptions were meant to detect a clinically meaningful difference. Since the result was statistically significantly different for the primary outcome using non-parametric statistical testing, we feel that the sample size was indeed sufficient.

8. Line 169-174 The authors addressed compliance both by reminder calls as well as return of the medication label with date and time.

9. Line 195-207 This was a good explanation of the descriptive data analysis and why appropriate comparative tests were chosen. It is easy to follow.
Results

10. Table 1 Was there more information on medication or other medical problems that would alter or delay visualizing ureteral efflux such as HTN, DM, medication including diuretics EBL and intraoperative IVF? If available this should be included.

We chose not to collect this data. The study was designed in a way to be applicable to usual practice, where these variables will exist and not be in the control of the operating surgeon.

11. Table 3 This is an important description of what was found if ureteral efflux was not seen. Please clarify if the end point was strictly timed and recorded as 3 min before the outcome of non visualization was determined.

The end-point of non-visualisation of the ureteral jet was not strictly timed. The manuscript has been edited to mention this.

12. Figure 2 Perhaps a picture side by side of all three colors to give the reader an idea of what the differences were visually.

This is a good suggestion, and the figure has been edited to show this.

Discussion:

13. This is a thoughtful review of the strengths and limitations of this study. The focus of using video with a separate blinded observer contributes to inter relater reliability at the same time. The authors should be commended for a meticulously designed trial.

Thank you for your thoughtful review of our manuscript. Your points are valid and we appreciate your comments that will improve our paper.

REVIEWER #2:

This is a double masked randomized control trial comparing riboflavin versus placebo for ease of ureteral patency following prolapse surgery. This well-written, straightforward trial compares a readily available, affordable over the counter medication to ease assessment of ureteral patency. The authors found through surgeon assessment and video review that riboflavin improved the ability to identify ureteral efflux. A few issues need to be addressed.

1. One issue that makes this study appealing is how cost effective riboflavin; given that indigo carmine may be available it would be helpful to have information on the cost of the other medications discussed, ie phenazopyridine, fluorescein

Cost figures are added to the manuscript.
2. How was compliance assessed beside patient writing the time and date they took the medication? Did 100% of patients report taking the medication as instructed?

Compliance was addressed by having the research assistance phone or text-message the subjects the night before surgery. Subjects took the study medications (vitamins) at home the night prior to surgery, so witnessed administration was not feasible. We assessed compliance by having subjects return the study medication envelopes. 100% of subjects reported taking the assigned vitamin capsules the night prior to surgery. We felt that the administration regime replicated what would occur in usual clinical practice.

3. Was this study registered on clinicaltrial.gov?

The study site is in New Zealand. The clinical trials registry in New Zealand is the ANZCTR, the Australian New Zealand Clinical Trials Registry. This clinical trials registry is accepted by the ICMJE and the WHO as an acceptable registry for clinical trials.

4. Were the other RCTs published on other medications for urinary patency used for the power analysis?

The other RCTs were not used to calculate our sample size. There are few RCTs published that assess the visualization of the ureter jets at cystoscopy. The two RCTs cited in this article were published after our study had been designed and implementation planned.

5. The authors need to add more discussion on the other RCTs that have been done on this topic

The discussion section was revised to discuss these trials in greater detail.

Thank you for your thoughtful and thorough review of our manuscript. Your suggestions will improve the quality of our paper.

REVIEWER #3:

This manuscript describes a RCT designed to compare ureteral patency assessment after PO riboflavin versus placebo.

The study idea is simple, and the execution of the study was very good.

The manuscript is well written and easy to follow.

I have no questions

Thank you for your review of our manuscript. We appreciate your comments.

STATISTICAL EDITOR’S COMMENTS:
1. line 61: Should round this to 0.71.

**Revised in the manuscript.**

2. lines 61-62: Study not powered to evaluate urinary tract injuries. 0/33 has 95% CI upper bound of 11%.

**This statement was removed from the abstract.**

3. lines 141-151: There was one primary outcome (color difference, lines 47-49), if the power analysis was designed to evaluate both color difference and "ease of visualizing the ureteric jets" (of which there were two hypotheses, then a stricter alpha value should be used, since a total of 3 hypotheses are being tested. Otherwise, should report the primary as color difference and the others (ease of visualization by two metrics and confirmation of bilateral ureteral patency were each secondary outcomes.

**The manuscript was revised to discuss the sample size calculation for only the primary outcome.**

4. Table 1: Since this was a RCT, there is no need to statistically compare the cohorts. Differences should be due to random chance.

**The p-value column has been deleted.**

5. In Tables of results, should clearly demarcate the stated primary from the secondary outcomes.

**The legend to figures has been updated to state primary or secondary outcomes.**

**Thank you for your review and helpful comments.**

Kind Regards,

Michael L. Stitely, M.D.
Hello Daniel.

Here are the responses to the listed points:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
   **I am happy with the changes.**

2. Please add in-text citations for both Figure 4 and the video in the main text of your manuscript.
   **Done: line 219 and line 259**

3. **LINE 54:**
   a. Please express this p-value and all the p-values in your paper to no more than three decimal places.
      **Done**
   b. Where is the p-value stated other than the abstract? The information must be contained in the body text, tables, or figures for consistency. **Line 215**

4. **LINE 56:** Where is the p-value stated other than the abstract? The information must be contained in the body text, tables, or figures for consistency. **Line 221**

5. **LINE 57:** Where is the p-value stated other than the abstract? The information must be contained in the body text, tables, or figures for consistency. **Line 227**

6. **LINE 178:** For articles submitted to O&G after July 1, 2018, we require a data sharing statement indicating what we've listed here. Your answers may be different from what I've listed here. If so, please edit the responses accordingly.
   **Edits made. The website containing the study data is listed on line 136.**

7. **LINE 189:** Table 1 is not meaningful enough to include and this line could be deleted.
   **Done. I have re-numbered table 2 to now be Table 1 (in the text and on the table).**

8. **LINE 207:** This tool was not mentioned in the Methods – please clarify
   **The Mann-Whitney and Wilcoxon rank sum test are the same test. I have edited the manuscript to use consistent nomenclature throughout.**

9. **LINE 322:** This information might be presented better as a list of information, or shaded box. “Both ureters seen after IV Fluorescein” repeats in the Placebo group – is this intended?
   **The information in this table/list is the result of further investigations when both ureters were not seen on cystoscopy. The repeat of “both ureters seen…” is intentional.**

One other point: The references after reference #2 have dropped out of the paper. This was some quirk of formatting, I think. I have attached a separate word document containing the references so that these can be added in and hopefully avoid formatting issues.

Thank you for considering our manuscript for publication.

Kind Regards,
Michael Stitely
Dear Dr. Stitely,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. Please add in-text citations for both Figure 4 and the video in the main text of your manuscript.
3. LINE 54:
   a. Please express this p-value and all the p-values in your paper to no more than three decimal places.
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Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the “Accept all Changes” function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on Monday, November 5th.

Sincerely,

-Daniel Mosier
Hello Stephanie.

The figures look great!

For AQ1: the version of Figure 2 without labels is attached.

For AQ2: Here are the y-axis labels
Figure 3: "Number of subjects"
Figure 4: "Number of subjects"

Thank you for your assistance.

Kind Regards,
Michael Stitely
To avoid a delay, I would be grateful to receive a reply no later than Thursday, 11/1. Thank you for your help.

Best wishes,

Stephanie Casway, MA  
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