Author’s response to reviews

Title: Influence of anesthesia methods on surgical outcomes and renal function in retrograde intrarenal stone surgery: a prospective, randomized controlled study

Authors:
Ohseong Kwon (kpoohk@gmail.com)
Jung-Man Lee (jungman007@gmail.com)
Juhyun Park (dr_jhpark@naver.com)
Min Cho (cmc1206@empas.com)
Hwancheol Son (volley@snu.ac.kr)
Hyeon Jeong (drjh@brm.co.kr)
Sung Yong Cho (kmoretry@daum.net)

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RE: Manuscript revision ID BANE-D-19-00396, “Influence of anesthesia methods on surgical outcomes and renal function in retrograde intrarenal stone surgery: a prospective, randomized controlled study”

Dear Editor,

Thank you for the comments on our manuscript. We have revised our previous paper based on the comments made by the reviewers. We hereby submit the revised paper. We are also sending a letter describing our replies to comments of the reviewers in a point-by-point fashion on separate sheets. We would highly appreciate it if you could review this paper again for publication in BMC Anesthesiology.

Sincerely Yours,

Sung Yong Cho, M.D., Ph.D.
Department of Urology
Seoul National University Hospital,
Reply to comments of the Reviewer 1

Hossam El-Beheiry (Reviewer 1): The manuscript analyzed the influence of anesthesia methods on surgical outcomes and renal function in retrograde intrarenal surgery (RIRS) in a prospective, randomized controlled study. The manuscript concluded RIRS under SA showed advantages in renal function change using Reno gram at postoperative 3 months and in lower pain score on the first postoperative morning. Performance of operator under SA was worse than that under GA and significantly improved with sedation. RIRS under SA showed advantages in lower pain score at postoperative first day.

Page 3, lines 26-28: Clarify what is meant by normal can have renal dysfunction.
Reply: Thank you for your comment. Renal dysfunction can happen even in patients who had normal renal function preoperatively. Choo et al. reported that 9 of 46 patients (19.5%) with normal renal function showed postoperative aggravation [1].

References


Page 3, lines 32-34: Provide necessary references that support the statement 'toxic effect of …'
Reply: Thank you for constructive review. We added the reference about renal effects of general anesthesia.

References


Page 5, lines 19-27: Was there any reason not to use a laryngeal mask airway instead of endotracheal intubation in this cohort of patient?
Reply: Thank you for your helpful review. In our hospital, we usually perform endotracheal intubation in the RIRS, so to reduce deviation and to maintain consistency. For RIRS, the patients are moved downward from a mechanical ventilator after endotracheal intubation. And then, lithotomy position is applied for surgery. Even though anesthesiologists can readjust the supraglottic airway device, which is already inserted intraoral space of the patients in most cases, the situation requiring endotracheal intubation after removal of the supraglottic airway devices
can occur during the surgery in some cases. If the situation would occur, endotracheal intubation could be difficult because the head of the patient is positioned in the middle of the operating table. Therefore, we usually perform endotracheal intubation in the RIRS.

Page 5, lines 36-42: What was the baricity of the local anesthetic used for spinal anesthesia? How abdominal circumflex and body mass index affected the doses of spinal anesthetics used?
Reply: Thank you for your constructive and helpful review.

At first, we use hyperbaric bupivacaine for spinal anesthesia in our hospital. For the dose of bupivacaine, we usually decide the dose of bupivacaine according to operation site as the top priority in our hospital. And we additionally consider the patient’s height. Even though there has been controversy in terms of influence of patient’s height on the block level, there have been several previous studies supporting relationship between patient’s height and the block level in spinal anesthesia. However, we did not use the abdominal circumflex and body mass index for determination of dose of bupivacaine. Also, we administrated bupivacaine with median 14 mg and range from 10-17 mg in our study. We miswrote the sentence (page 5, line 36-42) at the previous manuscript. Now, one author, who is the anesthesiologist, re-reviewed our previous manuscript. Finally, we revised the sentence as following;

The intrathecal position of the tip of the needle was confirmed by aspiration of clean cerebrospinal fluid, following which 10-17 mg (median: 14 mg) hyperbaric bupivacaine (Marcaine Heavy inj 0.5%, Astrazeneca, France) and 20 μg fentanyl were administrated intrathecally considering operation site and patient’s height.

Page 5, lines 51-53: What was the level of spinal blockade in this cohort of patients?
Reply: Thank you for your constructive review. According to your comments, we added some sentences in the first paragraph of results section as following;

Patient demographics and stone characteristics are shown in Table 1. Thirty-nine patients were assigned to the GA group, and 31 patients were assigned to the SA group. All of them completed this study trial. The blockade level of spinal anesthesia was between T2-T10 (number of T2/T3/T4/T6/T8/T10 in the SA group: 2/5/7/8/7/2). One patient complained mild discomfort of pain sensation during the surgery. His height was 178 cm and we injected 14 mg of bupivacaine and 20 μg of fentanyl intrathecally for spinal anesthesia, which leaded the blockade level was T10. We treated the patient with midazolam 5 mg and fentanyl 100 μg because the patient complained mild discomfort.

Page 6, line 4-7: State explicitly the primary and secondary outcomes of this study.
Reply: Thank you for your sharp comment. We added a sentence in the first paragraph of page 6 as following;
Patient characteristics included age, sex, body mass index, laboratory results, and other comorbidities. Stone characteristics included laterality, Hounsfield units, numbers, maximal size, and volume. Primary outcome is renal function change, and secondary outcome is performance of operator.

Page 6, lines 47-49: State the variables used to calculate the sample size.
Reply: Thank you for your constructive review. Although there was little evidence for this subject, the approximate figures were calculated from previous authors’ studies. So, we changed a sentence in the paragraph as following;

We planned a study of a continuous response variable from independent control and experimental subjects with one control(s) per experimental subject. We planned a study of experimental subjects with one control(s) per experimental subject.

Page 8, lines 50-56: Clarify the statement 'relative renal function'. Clarify what is meant by significant increase in relative renal function in the GA group more than the SA group while the previous sentence indicates that the SA group showed improvement more than GA group.
Reply: Thank you for your sharp comment. We changed “relative renal function” into “separate renal function” throughout the manuscript.

Page 9, lines 6-19: Indicate whether there was an association between the level of SA blockade and maneuverability, accessibility, and patient discomfort.
Reply: Thank you for your helpful review. However, it was difficult to consider all parameters. Especially, all surgeries were performed by single surgeon, so the objective description of subjective factors was limited. We think there should be more discussions about this in the near future.

Page 10, lines 8-9: Mention the major complications that occurred under GA and SA.
Reply: Thank you for your sharp comment. So, we changed the sentence in the paragraph as following;

Some studies reported that surgeries under regional anesthesia could show reduced major complications than those under GA. Some studies reported that surgeries under regional anesthesia could show reduced major complications (for example, mortality, morbidity, and myocardial infarction) than those under GA.

Page 10, lines 26-30: Change 'patient controlled anesthesia' to 'patient controlled sedation'.
Reply: Thank you for your kind comment. We changed the sentence as following;

Karacalar and colleagues suggested that spinal-epidural anesthesia along with intravenous patient-controlled anesthesia could be an alternative to GA. Karacalar and colleagues suggested that spinal-epidural anesthesia along with intravenous patient-controlled sedation could be an alternative to GA.
Page 10, lines 55-56: Clarify that references 24-26 were studies done in non-urolologic surgeries.

Reply: Thank you for your kind comment. We changed the sentence as following;

Some studies have reported GA as a risk factor for renal dysfunction after surgery. Some studies have reported GA as a risk factor for renal dysfunction after non-urolologic surgeries also.

Page 11, lines 35-44: Explain the reason for the results mentioned in these lines.

Reply: Thank you for your sharp comment. We mentioned the results to show the differences from existing researches in terms of evaluating renal function and operator’s performance.

We highly appreciate your invaluable comments and helpful suggestions.

Reply to comments of the Reviewer 2

Duane Funk (Reviewer 2): The paper by Cho et. al. is very interesting and is also relevant for clinical anesthesiologists. In my own practice I have often wondered if the type of anesthesia for this surgery had clinically important outcome difference. The authors should therefore be congratulated for completing this study. I think the study gives some interesting results, however there are some significant methodological results that preclude publication.

First, the trial, as registered at ClinicalTrials.gov, has listed as its primary outcome ‘renal function change using nuclear medicine tests’. The statistical analysis plan however, on p6 is very unclear as to how this study is powered. This section needs to be written with the power analysis clearly defined (not as it is now: ‘a continuous response variable ’; I am not sure what variable the authors are referring to).

Reply: Thank you for your constructive review. Although there was little evidence for this subject, the approximate figures were calculated from previous authors’ studies. So, we changed a sentence in the paragraph as following;

We planned a study of a continuous response variable from independent control and experimental subjects with one control(s) per experimental subject.

And the power was written in last paragraph at page 6.

Assuming that the trial is powered to look at differences in change in renal function then we must turn our attention to the results section, specifically table 2. The entire table 2 needs to be re-done, focusing on the primary outcome which is change in renal function. In this regard, the data for the nuclear medicine tests, that looked at change in renal function are very unclear (last 4 lines of data in Table 2). It is very unclear what the authors are measuring and what is being compared. Is this relative renal function per kidney? What are you comparing that you have p values for? I would eliminate these and just focus on the relative change between the operative sides (GA vs. SA) at the two time points.
Reply: Thank you for your constructive review. The nuclear medicine test was performed to evaluate relative renal function, and we tried to show the separate renal function got better after spinal anesthesia.

The other issue with table 2 is that you have over 20 comparisons between SA and GA. You set the alpha value at 0.05, but you have a major issue with multiple testing. As a result, if you do 20 t-tests with an alpha of 0.05, you are likely to get a ‘positive’ result, i.e. P&lt;0.05 by chance. If you want to keep this many comparisons, then you should use Bonferroni’s correction (0.05/N ; where N=number of t-tests). Doing this leads to a corrected p value of 0.002, which would make all of these tests in table 2 non-significant. I would suggest the authors re-think their analysis plan or consult a statistician before re-submitting this work.

Reply: Thank you for your constructive review. The parameters do not affect each other, so authors think that this analysis is suitable for the study.

I would also eliminate Table 3 completely. The results are completely non-blinded and the scoring system is very subjective and the intervals are not meaningful (is a 5 really that different from a 6)?

Reply: Thank you for your constructive review. In this study, the surgeon predicted a significant increase in discomfort caused by respiration during SA, but differences were not so significant. In particular, it was very difficult to show that the differences had decreased under epidural block, so authors had to use subjective parameters. RIRS surgeons clearly feel the difference of breathing discomfort.

I think this paper has merit. I would focus on two outcomes specifically. First, the relative change in renal function on the operative side between SA and GA. The authors then need to focus the discussion on why there is a change that is significant at 3 months but not on the first postoperative day. The other really interesting outcome, which can only be a secondary outcome because the trial wasn’t powered for this, is the stone free rate. This is very interesting as the rate is much higher in the GA group. This is despite the fact that the surgeon rated his conditions as only ‘so-so’ for the GA group. As I had mentioned, the surgeon’s opinion scale isn’t really valid, but it does give interesting and conflicting results.

Minor Comments

- p3 36 and 38 abnormalities instead of abnormality
Reply: Thank you for your kind comment. We changed the word as you advised.

- p5 L42 circumference instead of circumflex
Reply: Thank you for your kind comment. We changed the sentence at the paragraph as following;

The intrathecal position of the tip of the needle was confirmed by aspiration of clean cerebrospinal fluid, following which 13-14 mg bupivacaine and 20 μg fentanyl were administrated intrathecally according to patient’s sex, height, abdominal circumflex, and body mass index. -&gt; The intrathecal position of the tip of the needle was confirmed by aspiration of
clean cerebrospinal fluid, following which 10-17 mg (median: 14 mg) hyperbaric bupivacaine (Marcaine Heavy inj 0.5%, AstraZeneca, France) and 20 μg fentanyl were administrated intrathecally considering operation site and patient’s height.

• p5 L48 remove failed
Reply: Thank you for your kind comment. We removed “failed”.

• p5 L53 ‘according to patient’s lead’. What does this mean?
Reply: Thank you for your comment. It means that sedation was applied to wanted patients only.

• p6 L15 what formula for eGFR was used?
Reply: Thank you for your sharp comment. We commented at the end of page 11 that the authors used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based equation or the Modification of Diet in Renal Disease (MDRD) Study equation.

• p6 L33 Need a definition for fluctuations.
Reply: Thank you for your constructive review. We defined the blood pressure fluctuation as a change of more than 20% of the baseline systolic blood pressure in the ward before the surgery in this trial. Therefore, we revised the sentence as following:

Intraoperative incidents associated with anesthesia (blood pressure fluctuation, nausea, and pain) were documented. Blood pressure fluctuation was defined as a change of more than 20% of the baseline systolic blood pressure in the ward before the surgery in this trial.

• Table 1 need units for Cr and eGFR. No P value needed for the baseline values. If randomization was sufficient then any differences between groups are by chance. Since there is a difference in baseline eGFR, you probably should ask a statistician for how to correct your renal function results for the baseline eGFR differences. This is very important as your outcome is renal function and this baseline difference could influence your results. I would suggest multiple logistic regression with eGFR and the presence of diabetes and hypertension at baseline as the variables.
Reply: Thank you for your constructive review. We added units for Cr and eGFR, and removed P values for baseline values.

We highly appreciate your invaluable comments and helpful suggestions.

- END -