Author's response to reviews

Title: Comparing the efficacy of mydriatic cocktail-soaked sponge and conventional pupil dilation in patients using tamsulosin - a randomized controlled trial

Authors:

Janos Hargitai (janos.hargitai@rn.dk)
Laszlo Vezendi (laszlo.vezendi@rn.dk)
Joergen Vigstrup (joergen.vigstrup@rn.dk)
Finn Eisgart (eisgart@rn.dk)
Balint Hargitai (hargitaib@gmail.com)
Henrik Vorum (henrik.vorum@rn.dk)

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Author's response to reviews: see over
Dear Editor,

Thank you for sending us the peer reviews and constructive comments regarding our manuscript: “Comparing the efficacy of mydriatic cocktail-soaked sponge and conventional pupil dilation in patients using tamsulosin - a randomized controlled trial” MS: 1050222216866118.

We have carefully followed every issue raised by the reviewers and the editor.

Our response as follows:

Editorial comment:

Please include an Acknowledgements section in your manuscript.

We included an Acknowledge section in our manuscript:
“Henrik Vorum is a recipient of The Bagger-Sørensen Research Fondation.” (page 12)

Referee 1

”The way that the conclusion is worded, it may confuse some readers into thinking that the mydriatic sponge is a superior method for tamsulosin patients, when in fact the study shows no difference. Therefore, I would ask the authors to re-word the conclusion ... to say that this method did not provide a clinical difference or benefit compared to eyedrops alone. The convenience and efficiency can be discussed, but should not be a part of, or basis of, the conclusion.”

We have re-worded our conclusion:

„In conclusion we have found that using a mydriatic cocktail-soaled wick – an alternative way to achieve intraoperative mydriasis for cataract surgery – was as effective and safe as the conventional repeated eyedrops regiment in tamsulosin using patients. Though this method did not provide clinical difference or benefit compared to the conventional method, it may serve as a safe and timesaving alternative preoperative protocol even for high risk tamsulosin treated patients. „

(Conclusion: page 12)
Referee 2

General comment

“However, the statistical analysis and results section need to be significantly improved to determine the potential hidden in the data.”

We consulted a senior biostatistician (SLC), rewrote statistical analysis section in the methods section and reanalysed our data.

Statistical analysis

“The size of the study was decided from the following power considerations. With 25 patients in each of two groups, a 0.8mm difference between groups will be recognized by an unpaired t-test with 80% probability assuming a within group standard deviation of approximately 1mm.

Differences in general between groups (age, pupil diameter, miosis, operation time) were analyzed with a one-way analysis of variance (ANOVA), and differences between specific groups (group 1 vs. group 2 and group 1 vs. group 3) were assessed by suitable contrasts assuming normality and variance homogeneity. Mean and 95% confidence intervals are given for each comparison. Normal distribution was assessed by qq plots and variance homogeneity by robust variance test. Differences between groups in proportions (hypertension, diabetes, clear corneal incision location, IFIS signs, complications and use of iris retractors) were assessed by Fisher's exact test.” (Statistical analysis: page 7)

• Major Compulsory Revisions

“1. Using permuted blocked randomization is useful with small sample size. However, the authors must provide the size of the blocks used. If these were small, block adjusted statistics (such as Contingency Chi2 test for categorical variables, stratified ANOVA and linear rank test for continuous variables) need to be performed to overcome the intra-block correlations (i.e. R). These can be ignored if the sizes of the blocks are large. Hence the authors must mention the size of the blocks. (see attached supplement material on blocked randomization and analysis of results)”

We reanalysed our results using ANOVA and Fisher's exact test. (Results: page 8; Table 1: page 17, Table 2: page 18)

“2. A more detailed description of the masked randomization would be appreciated. Exactly how the randomization was executed. The surgeon not being masked is a big drawback in the study design (mention this in the methods as well). However, were the surgeons involved in the dilatation process or were they only operating?”
Randomisation method was corrected:

“The study group was subdivided randomly into two equal sized groups (n=30), using sealed envelop method. The randomization was carried out by the anaesthetic nurse in the anaesthetic room. Surgeons were masked for the randomisation but not for the use of tamsulosin due to regional safety guidelines.” (Methods/Patients; page 5, line 6-9)

“Surgeons were not involved in the dilatation process.” (Methods/ Preoperative preparation; page 6, line 9.)

“3. Please mention the type of anesthesia used for cataract surgery. A retro/peribulbar block can cause pupillary dilation by itself which may potentially confound the results.”

In the two mydriatic cocktail-soaked sponge group (group 1 and group 3) we used topical anaesthesia of oxybuprocain 0.4% 3 times: before inserting the sponge in the outer lower fornix, before inserting the specula, and before initial wound construction. The mydriatic cocktail also contained oxybuprocain 0.4%, which could diffuse into the ocular tissues from the sponge for 30 minutes. (Methods/Preoperative preparation: page 5, subline 1-4 and page 6, line 1-5; Methods/ Surgical technique and intraoperative measurements: page 6, subline 1-2)

In the conventional repeated eyedrops group (group 2) we also used topical anaesthesia of oxybuprocain 0.4% 3 times: before inserting the sponge in the outer lower fornix, before inserting the specula, and before initial wound construction, along we the 3 drops of oxybuprocain 0.4% with 10 minutes interval. (Methods/Preoperative preparation: page 5, subline 1-4 and page 6, line 8-9; Methods/ Surgical technique and intraoperative measurements: page 6, subline 1-2)

“4. While reporting percentages, please use a decimal point i.e. a dot rather than a comma (see introduction)”

We corrected percentages with decimal point throughout the manuscript.

“5. I recommend performing 2 sets of statistics i.e. between group 1 and 2 & then between group 1 and 3. This will answer the following 2 questions:
   a) Whether cocktail with or without wick is better in eyes with tamsulosin and
   b) Whether eyes with tamsulosin differ from normals using wicks in both groups.”

We reanalysed results date after suggestion, performing 2 sets of statistics: between group 1 and group 2, then between group 1 and 3. (Methods/Statistical analysis: page 7; Results: page 8; Discussion: page 9-12; Table 1: page 17; Table 2: page 18)
"6. In the results section, many p values are lacking. As per Table 1, the authors seem to have compared all 3 groups simultaneously. There should be one more column for p value for each row. Comparing 3 groups cannot be done with student T test as mentioned by authors. It requires Kruskal – Wallis or ANOVA which is not mentioned by the authors.”

We subdivided our results into preoperative results (Table 1: page 17) and intraoperative results (Table 2: page 18). We included p values for each comparison between group 1 and group 2, and group 1 and group 3 respectively.

"Differences in general between groups (age, pupil diameter, miosis, operation time) were analyzed with a one-way analysis of variance (ANOVA).”

"Differences between groups in proportions (hypertension, diabetes, clear corneal incision location, IFIS signs, complications and use of iris retractors) were assessed by Fisher's exact test.” (Statistical analysis: page 7)

"7. The authors have divided the pupillary size into 3 categories (ordinal variable). Comparing these across groups requires Chi2 (Contingency Chi2 test for blocked randomized data). This is not mentioned and there are no p values comparing poor, sufficient and satisfactory mydriasis between the 3 groups at the 3 time points. These parameters could perhaps be shown in a graph (bar or boxplot) for easy comprehension by the readers.”

After consulting a senior biostatistician (SLC), due to its subjective categorization we excluded data with 3 categories for pupillary size from our manuscript.

"8. The authors mention in methods that they have used multiple regressions. However, there is no evidence of this in the results section, except for the last line of results. Please mention whether linear or logistic regression was performed. If logistic regression was used, please mention whether ordinal or multi-nominal logistic regression was used (as outcome is ordinal)? Also please provide a table showing results from univariate and then multivariable analysis to show which variables were considered and how the multivariable models were set up. I recommend performing separate statistics between groups 1 and 2 and then between groups 1 and 3 (see above). Regression analysis is not a must for such a small data set and may be omitted by the authors if not feasible.”

Following consultation with a senior biostatistician (SLC), we excluded regression analysis data from our manuscript. Correlation between total intraoperative miosis and operation time might have been influenced by other factors such as the hardness of the nucleus (phaco time), folding of the IOL etc.
• Minor Essential Revisions

“1. The sentence starting with “Histologic examination of cadaveric eyes with history of tamsulosin treatment showed a decreased iris dilator muscle thickness ….” is not relevant to the study and is out of context in the introduction. This may be deleted.”

This sentence along with the reference was deleted from the manuscript.

“2. Spelling mistakes need to be corrected. Eg, “horisontal chop”

Spelling mistake was corrected (Methods/ Surgical technique and intraoperative measurements: page 6, subline 6).

“3. Suggest using STATA or SPSS for statistics with a statistician to improve results and discuss the new results appropriately”

We used STATA, version 11 and consulted senior biostatistician (SLC). (Methods/Statistical analysis: page 7; Results: page 8; Discussion: page 9-12; Table 1: page 17; Table 2: page 18)
Referee 3

Major Compulsory Revisions

“1. If the authors’ purpose was to investigate the effect of a mydriatic-cocktail soaked cellulose sponge on perioperative pupil diameter in tamsulosin-treated patients undergoing elective cataract surgery, why they included control patients not taking any #1 adrenergic receptor inhibitors? Previous studies indicated that the use of a wick pre-soaked in standard mydriatic and non-steroidal anti-inflammatory drugs was as effective or superior to the conventional repeated instillation of drops before cataract surgery.”

We compared the efficacy of mydriatic cocktail-soaked sponge and conventional pupil dilation in patients using tamsulosin. However we believe by adding a control group without any α₁ adrenergic receptor inhibitor treatment, we could answer the following questions:
   a. Whether our "cocktail" with or without wick works better in patients with tamsulosin treatment?
   b. Whether patients with tamsulosin treatment differ from patients without any α₁ adrenergic receptor inhibitor treatment using wicks in both groups?
To our best knowledge no study addressed these questions to date.

“2. There is no sample calculation.”

Sample calculation was included in the Methods section:
“The size of the study was decided from the following power considerations. With 25 patients in each of two groups, a 0.8mm difference between groups will be recognized by an unpaired t-test with 80% probability assuming a within group standard deviation of approximately 1mm.”
(Methods/Statistical analysis: page 7)

“3. I suggest a table summarizing the demographic data. Please include gender. This table must include a column with the “P” of each variable.”

We corrected our Methods section stating that all study subjects were male. (Methods/Patients: page 4, lines: 1-4.)
We subdivided our results, and added an extra table (Table 1), with our preoperative data. (Table 1: page 17). In both of our tables we included p values (Table 1: page 17; Table 2: page 18)

“4. I suggest a flow chart diagram (ex.: CONSORT flow chart).”

We prepared a CONSORT flow chart diagram as supporting file.
“5. It’s important to include all statistical analysis comparing the difference between the groups (age, hypertension, diabetes, gender, Preoperatively/After nucleus delivery/Before IOL implantation pupil diameter grading, mean operation time, )”

We included all statistical analysis comparing differences between groups. (Results: page 8; Table 1: page 17; Table 2: page 18)

“6. The table of intraoperative data must include an additional column with the “P” of each variable.”

We included an additional column with p values for each variable. (Table 1: page 17, Table 2: page 18)

“7. The sentence “There was no significant difference in pupillary diameter preoperatively and after nucleous delivery, however before IOL implantation, pupil was significantly smaller in group 1 as compared to group 3 (p=0.0084)” is not necessary if the table intraoperative data include the “P”.”

The above sentence was excluded from our manuscript. (Results: page 7)
Referee 4

Major Compulsory Revisions

“In surgical technique, the authors reported that used either oblique or temporal clear corneal incision. Please define how many patient in each group. Oblique incision is closer to the central cornea, thus in those patients iris prolapse from the wound may occur more frequently compared to the temporal group. Thus I believe that these two different incision locations should be included in different groups.”

We now have defined how many patients we had in each group. There was even distribution of temporal and oblique clear corneal incision in all 3 groups. (Table 2: page 18) Normal distribution was assessed by qq plots and variance homogeneity by robust variance test. (Methods/Statistical analysis: page 7, subline 7-8). This uniform distribution limits observational bias between groups, and therefore we have not subdivided our results into two separate groups in respect of wound location. However there are certain surgical considerations for safe wound construction to minimize the risk of iris prolapse, that are now included in our discussion. (Discussion: page 9, line 20-25)

“The results are not given orderly. Following results, which are mentioned in Discussion, should be moved to the Results section:
- We observed statically significant miosis in tamsulosin treated patients (group 1) compared to patients without #1-ARA medication (group 3) only before IOL implantation (p=0.0084).”

The above sentence was removed from our Discussion and results are shown in Results (page 8) and Table 2 (page 18).

“o In the two tamsulosin treated groups, the patients dilated with a mydriatic wick had greater preoperative mydriasis in comparison with patients receiving conventional eye drop regimen, however, this difference was not significant. This slight difference disappeared at later stages of surgery.”

The above sentence was moved to Results section (page 8).

“o The duration of the operation was significantly correlated to intraoperative miosis only in our control group, but not in the two tamsulosin treated group.”

Following consultation with a senior biostatistician (SLC), we excluded regression analysis data from our manuscript. Correlation between total intraoperative miosis and operation time might have been influenced by other factors such as the hardness of the nucleus (phaco time), folding of the IOL etc.
“• Were patients, in whom iris retractors were used, included in the statistical analysis. I believe that the incidence of iris refractor use which is on page 7 is important. However, patients with iris hooks should be excluded from the statistical analysis.”

We expanded our methods with the following sentence: “In case of iris retractor use, patients were excluded from further pupillary measurements, and statistics.” (Methods/Surgical technique and intraoperative measurements, subline: 14-15)

“• Please give the p values for all comparisons.”

P values are now given for all comparisons. (Results: page 8; Table 1: page 17; Table 2: page 18)

Minor Essential Revisions

“Please write ARA in full when it is first appearing in the text.”

$\alpha$-ARA is now written in full when it is first appearing in the text. “Intraoperative floppy iris syndrome (IFIS) associated with tamsulosin – a systemic $\alpha_1$ adrenergic receptor antagonist ($\alpha_1$-ARA) - was first described by Chang and Campbell in 2005.” (Background: page 6, line: 6-7)

“Pupil diameter was measured with 0.5 mm intervals. Please explain this.”

We corrected the above sentence: “Pupil diameter was measured with 0.5 mm increments in the horizontal plain preoperatively, after nucleus delivery, and before IOL implantation using Geuder Castroviejo caliper (Geuder AG, Heidelberg, Germany).” (Methods/Surgical technique and intraoperative measurements: page 6, subline: 11-13)

“• On table 1, since iris billowing and iris prolapsed are observed parameters of IFIS, observed pupil constriction could also be added as a different parameter from intraoperative miosis (which is an objective measured parameter in this study).”

We have now added pupil constriction measurements to our study. (Table 2: page 18)

“• It was noted as “Satisfactory or sufficient mydriasis was observed throughout the surgery in 16/27 patients in group 1, 17/26 patients in group 2, and 30/30 patients in group 3.” However, this is not in accordance with their results. Five patients in the control group had poor pupil dilation before IOL implantation. Also, iris retractors were used in one patient, so this patient ought to be excluded from the final results.”

After consulting a senior biostatistician (SLC), due to its subjective categorization we excluded data with 3 categories for pupillary size from our manuscript.
“• It is written as “In our control group we found significant correlation between total intraoperative miosis and operation time (p=0.007).” What about the study group?”

Following consultation with a senior biostatistician (SLC), we excluded regression analysis data from our manuscript. Correlation between total intraoperative miosis and operation time might have been influenced by other factors such as the hardness of the nucleus (phaco time), folding of the IOL etc.

We are looking forward to your favorable consideration for publication in BMC Ophthalmology.

Sincerely yours,

János Hargitai et al