Author’s response to reviews

Title: Leg elevation decreases the incidence of post-spinal hypotension in cesarean section: a randomized controlled trial

Authors:

Ahmed Hasanin (ahmedmohamedhasanin@gmail.com)
Ahmed Aiyad (dr.ahmed_aiyad@hotmail.com)
Ahmed Elsakka (ahmedsakka@hotmail.com)
Atef Kamel (Menna_atef01@yahoo.com)
Reham Fouad (rehamfouad@rocketmail.com)
Mohamed Osman (mosman55@yahoo.com)
Aly Mokhtar (alyaly4444@gmail.com)
Sherin Refaat (sherin.refaat@hotmail.com)
Yasmin Hassabelnaby (yalnaby@yahoo.com; yalnaby@kasralainy.edu.eg)

Version: 1 Date: 01 Feb 2017

Author’s response to reviews:

Dear Editor

We are grateful to the robust revision provided by the two reviewers. The meticulous revision improved our article. We provided all the requested details and correction. We answered all the reviewer comments hoping to meet their expectations.

Reviewer reports:

Reviewer 1: This is a very well written manuscript. I have no comments on the presentation of the study. Very well done. The design is straightforward, well analyzed, and appropriately presented. The study is somewhat dated given the current state of the art of managing hypotension and spinal anesthesia. However, I think the data from the study are useful presented in the appropriate perspective. My comments and suggestions are as follows:
* There used to be a major focus on trying to increase intravascular volume (leg wrapping/fluid loading/colloids/etc.) to prevent hypotension because there was an association between more hypotension, more ephedrine use, and more fetal acidosis. When it was determined that ephedrine was the significant cause of the acidosis, then the focus switched to studying the optimal use of phenylephrine. I assume the use of ephedrine in this study was due to lack of availability of phenylephrine or another alpha agonist. That needs to be discussed.

Response

We clarified this in the limitations in the discussion

* Since hypotension that is appropriately reversed pharmacologically is not much of an issue for the fetus or mother, the usefulness of leg raising needs to be put in proper perspective. Possible points of discussion:

  o Low resource settings where ephedrine is the only available pressor.

  o Rescue from profound hypotension after induction. For example, if the pressure falls rapidly, reversing with pressors AND leg raising.

Response

Both points were mentioned in the discussion at the end of paragraph no. 6.

Reviewer 2: GENERAL COMMENTS:

- This randomized study aims to investigate the use of passive leg raising (versus control) just AFTER onset of spinal anesthesia for elective Cesarean section on incidence of hypotension.

- The strengths of the study are the following:

  1. it is a randomized controlled study with an adequate sample size calculation (p 6) including 75 parturients / group.

  2. the use of passive leg raising (or more accurately "leg elevation" in the present study) after spinal anesthesia to try to prevent hypotension during Cesarean section has been investigated only once 23 years ago (ref. 9 quoted by the authors) and yielded a negative result but likely because of inadequate power (hypotension incidence of 39% vs. 53% in the control group with n=32 vs. n=31 parturients).
3- the present study retrieves conversely a positive effect of leg elevation (35% vs. 59%), which is an interesting finding, because it is a simple and no-cost maneuver particularly in low-resource countries.

- But there are also weaknesses:

1- a RL pre-load (10 ml/kg) was used whereas this is ineffective and clearly no longer recommended. Most experts recommend using a crystalloid co-load or a colloid pre-load (Ngan Kee, Curr Opin Anaesthesiol 2010 - Mercier, Curr Opin Anaesthesiol 2012 - Mercier Br J Anaesth 2014)

Response
We clarified this in the limitations of the study at the end of the discussion. It is to be mentioned that although co-loading is superior to preloading, the incidence of post-spinal hypotension is still high with all fluid loading regimens.

2- the vasopressor used is ephedrine, whereas there is a wide consensus since a decade at least to using phenylephrine (instead of ephedrine) as first-line vasopressor in elective Cesarean section. This is probably due to unavailability (or cost issue?) of phenylephrine in Egypt but nevertheless this limits the external validity of the present study for high-income countries where prophylactic phenylephrine + effective crystalloid coload or colloid preload are used.

These limitations need to be better detailed and acknowledged in the Discussion section of the manuscript.

Response
We addressed this point in details in the limitations of the discussion.

SPECIFIC COMMENTS:

Introduction:

* 3rd and 4th sentences (Lines 8 to 18):

The 3rd sentence is correct, i.e., "decreased vascular tone (due to spinal-induced sympathetic blockade) leading to decreased systemic vascular resistance and decreased venous return". But consequently, the next sentence (4th) is inappropriate, because increasing vascular tone by vasopressors not only increases systemic vascular resistance (via its action on arterial tone) but
also increases venous return (by constricting capacitance vessels, namely on the splanchnic venous system) (see Ngan Kee et al., Anesthesiology 2015 Apr;122(4):736-45 with the Discussion section in page 742)

Thus, increasing venous return may be achieved both with vasopressor and fluid administration. Please, modify accordingly.

Response, the sentence was rephrased

* Lines 26 to 36 :

The Passive Leg Raising (PLR) maneuver has been described by intensivists (your ref. 5 & 6 are adequate) : it is a well defined / specific maneuver where the whole body is lowered from the semi-recumbent position to the supine position, by titling the bed (see Fig. 1 in your ref. 6 where Monnet and Teboul describe precisely the maneuver). Thus, what you described here in the introduction along with your ref. 5, 6 & 7 is actually the PLR maneuver but contrarily to what you suggest in your last sentence, this is not what you have been using in your study. Indeed, as detailed in your Methods section at the top of page 5, you did not tilt the whole body of your parturient but rather only raise their legs for 30 cm using two standard pillows. This is a maneuver rather similar to the one described by Rout et al. in 1993 (your ref. 9) and it will be more appropriate as he did to entitle it as "leg elevation". This nuance is not purely semantic because the full PLR maneuver (which also include the trunk tilting) is likely more effective to mobilize venous blood from the large splanchnic compartment than leg elevation alone (see Monnet and Teboul, Crit Care 2015 Jan 14;19:18).

It is not a problem that you used a simple leg elevation maneuver in your study instead of the PLR maneuver per se, because obviously the latter cannot be performed easily in this Cesarean section setting. But you need to modify your manuscript to remove this potential confusion/misunderstanding.

Response

We modified the description of the maneuver from (passive leg raising) to (leg elevation) in the title, abstract, and manuscript.

It will be also useful/interesting that you provide the average angle obtained with the leg elevation you used.

Response
The angle of elevation it was added. However, we should point out that the precise angle was not constant because it varies according to the length of patient legs.

Methods :

* Page 4, line 37 : As I mentioned in my general comments, Ringer's lactate pre-load is no longer recommended (although still too much used routinely) because it has been well-shown to be poorly effective or ineffective and even potentially counterproductive (Ngan Kee, COIA 2010 - Mercier, COIA 2012 - Mercier BJA 2014). Thus, you should acknowledge this limitation in the Discussion section (pages 10-11).

Response

We clarified this in the discussion.

* Page 4, line 46 : please, remove the capital letter of "Bupivacaine" (i.e., write "bupivacaine") and change "ug" to "µg" (or "mcg").

Response : corrected

* Page 5, line 27-28 : please, convert "drops per minute" to international units (for ex : units / h).

Response:
corrected

* Page 5, line 36 : demographic data are not (secondary) "outcome" parameters ; they are "baseline" data.

Response :
Corrected

* Page 5, line 48 : an interval of 3 min for arterial blood pressure recording is a too long interval to optimally detect hypotension from onset of spinal anesthesia during Cesarean section until delivery of the newborn. All or at least most studies on spinal anesthesia for
Cesarean section have used a 1-min interval. This should also be acknowledged as a study limitation in the Discussion section.

Response:

This was mentioned in the limitations.

Results:

* Table 1: Please, provide the p value, even when "NS". For example, Nausea & Vomiting is probably less in the "PLR" group (this would make sense, given that hypotension incidence and ephedrine requirements are both less) but does not reach statistical significance likely because of insufficient power on this secondary outcome.

Response:

All P values were provided.

Discussion:

* Page 9, line 10: "this means that PLR decreased the incidence of hypotension by 63%". It seems you are making confusion between odds ratio and relative risk. The incidence of hypotension in your study decreased from 58.7% to 34.7% as shown in your Table 1. This means that it decreased by (0.587 - 0.347) / 0.587 = 0.409 = 40.9% (not 63%).

Response

Corrected

* Page 9, lines 12 to 15: this last sentence of the 1st paragraph appears useless; it is methodological information you already provided adequately in the Methods section (in the middle of page 5 along with the definition of the primary outcome).

Response: removed

* Page 9, 2nd paragraph: again, as I mentioned already above, please use "PLR" only when you refer to the actual PLR maneuver described in the literature you are quoting. But as soon as you refer to the maneuver you used in your study, please use "leg elevation" instead.
Page 9, line 38: I was unable to retrieve the 150-mL volume of blood mobilized from the calves" that you are mentioning here. In the study you quoted (ref. 8) of Rutlen et al. (Circulation, 1981), it is stated that leg elevation produced a 34 ± 4% decrease in counts from the radiolabeled intravascular space (with the counts being proportional to blood volume). Please explain where you find the information on the "150-mL volume of blood mobilized from the calves" you mentioned or alternatively modify your manuscript if inaccurate.

Response:

We mentioned that leg elevation produced a 34% decrease in counts from radiolabeled IV space. We also added a new reference that mentioned that this value is corresponding to 150 mL (reference number 9).

Page 10, line 41: I guess you intended to write "the use OF expensive and sophisticated…"

Response: corrected

Page 10, one line below: I agree it is "simple, rapid and effective". However you should make more clear in this comment, that the effectiveness, although well proven here, is not huge (nor mild): it is moderate (a decrease by 41% of the incidence of hypotension, with ephedrine requirement that are halved but unexpectedly low even in the control group).

Response:

We added this in the same paragraph in the discussion (paragraph no 6)

You may also add in this Discussion section that the (true) PLR maneuver has been already investigated (and quote Meirowitz et al., IJOA 2012; 21 : 324-8) in parturients undergoing Cesarean section but solely to try to predict hypotension (rather than to prevent it like in the present study) and in this case, it was found ineffective.

Response:

The reference was added
Response

All the previously mentioned limitations were provided.