Author’s response to reviews

Title: Prolonged Versus Brief Balloon Inflation During Arterial Angioplasty for De-Novo Atherosclerotic Disease: Protocol for a Systematic Review

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Author’s response to reviews:

I greatly appreciate the time and effort that you took to review this article. We have incorporated each suggestion into the revised manuscript. Please see specific responses to your comments below.

Reviewer #1: Thank you so much for the opportunity for reviewing this manuscript SYSR-D-18-00363

First of all, this is a well-written manuscript that provide an systematic process of thought about this particular intervention. however, the title of manuscript does not follow with PICO guideline and would bring about a confusion which category of the patient problem would be addressed by this work. As such, I would recommend the author to revise the title of the manuscript. For an example, angioplasty is too general terms to define the procedure as different vascular territory intervention yield substantial result and long term prognosis. Also, type of balloon, saying that coated or uncoated, would definitely affect the result by angioplasty. This more specific scope would let the interventionist fully adopt the protocol to do further study. Based on the fact that interventional angioplasty result depends on multifactorial factors, one of them, other than operator experience, is device or tools that facilitate the procedure. This equipment has been continued developed and this factor should be included in this protocol.

Please provide brief explanation while a duration of 1 minute has been employed as the cut-off value for the study group of prolonged angioplasty. There should be some prior evidence of
irreversible damage in any component of vascular wall that make the difference compared to those with shorted balloon angioplasty.

• Title

o Thank you for this comment. We have altered the title to better represent the PICO question. We will address the vascular territory in the body of the manuscript;

- In regards to the vascular territory, we have chosen to include all vascular beds but have a pre-specified subgroup analysis planned to stratify these studies based on vascular territory.

- Several other reviewers also identified concerns regarding the specific type of angioplasty devices used (drug coating, cutting, etc.). We have chosen to include all types of angioplasty devices in the initial search, however will perform subgroup analyses on these different variations of devices if they should arise.

• Justification of 1 minute duration

o The duration of 1 minute was initially a relatively arbitrary duration used in several benchtop and animal studies, however this duration demonstrated arterial damage. We have included a description and reference to these papers in the background to describe why 1 minute is our study cut-off. To our knowledge, there is no histological evidence of different magnitude of arterial injury based on different inflation times. However, there is clinical evidence, which is the focus of our review.

Reviewer #2: Rockley et al present the protocol for a systematic review of prolonged balloon inflation for arterial angioplasty in different arterial beds.

Angioplasty alone remains an important treatment option in peripheral arterial disease while it is no longer employed without stent implantation in coronary circulation.

Sufficient controversy exists to warrant a systematic review. The protocol is overall well written but can be improved in the following manner:
1. Angioplasty alone is rarely performed in native coronary artery disease; it is routinely followed by stent implantation. Thus, studies of angioplasty alone in coronary circulation are likely to be older. As one can expect, differences in engineering characteristics of earlier generation balloons may provide a residual stenosis/dissection rate that may not be relevant in the modern era. Similarly differences in medical therapy may effect clinical outcomes. It would be best to analyze and report these outcomes in two eras - say, prior to year 2000 and on or after 2000.

2. Similarly, the authors will discover studies in the pre-stent coronary literature using perfusion balloon catheters (which allowed very prolonged inflations by providing perfusion in the distal coronary bed). These catheters are no longer used on coronary angioplasty and these studies should be analyzed separately.

3. Will studies of inflation time in in-stent restenosis be excluded?

4. Reference 7 (Hovasse et al) studied inflation time in stent balloon implantation and not angioplasty. This should be removed since the objective is angioplasty balloon inflation time; not stent balloon inflation time.

- Stratify by Era (pre-2000 and post-2000)
  - This is a valid point and we will stratify our report of outcomes into different eras.

- Stratify by Device (perfusion balloon catheters)
  - This is another valid point that has also been raised by other reviewers, and we will also stratify our analysis by device.

- Inclusion of treatment on restenosis
  - Other reviewers also identified concerns regarding the treatment of restenosis. We have specified and justified that we will only examine de-novo stenoses.

- Reference 7 (Hovasse)
  - We have removed this reference; while it is related, it is not directly applicable to our topic of investigation.
Reviewer #3: Rockley et al., propose a protocol for a systematic review on prolonged balloon inflation for arterial angioplasty which is a fundamental treatment for atherosclerotic disease in the cardiac, cerebrovascular, and peripheral vasculature since its first use in 1977. The study aims to investigate whether an angioplasty balloon inflation of at least a minute duration, when compared with less than a minute balloon inflation, affects residual stenosis after arterial angioplasty, with an ultimate intention to synthesize the evidence and guide future clinical decision making and investigation.

The protocol is well thought-out with a clear objective, thorough methods and overall well written manuscript.

I have the following comment to the authors,

Background:

- Page 3, 2nd paragraph,

- The authors wrote 'Various techniques have been proposed to minimize restenosis following angioplasty, however many have not been thoroughly evaluated in randomized trials. One such technique is prolonged angioplasty balloon inflation time, which is theorized to reduce post-interventional dissection and induce smooth muscle dysfunction, thereby reducing vasospasm and resulting stenosis. Is there any prior literature on this? Can authors provide a reference?

- Reference the theorized risks of arterial injury following balloon inflation

  Thank you for this comment. Beyond our references 3 (Lantis et al) and 4 (Consigny et al) in the following sentence, this appears to be a theory without supporting histological evidence. This certainly is a fundamental concept of our study and we have now referenced and described articles that describe the histological negative impacts of angioplasty on arteries. However, the benefits of prolonged angioplasty appear to be theoretical and primarily supported by results of clinical trials which are the focus of our current study.
Reviewer #4: In the systematic review, the authors will evaluate the efficacy of prolonged balloon inflation over 1-minute duration to achieve the procedural success and improve the long-term vessel patency, compared with brief balloon inflation for 1 minute or less. Although current studies have reported the efficacy of metallic stents in atherosclerotic lesions, balloon angioplasty is still a standard treatment in patients who can not be treated without stent implantation. The optimal inflation time of balloon dilatation is still unknown in cardiac, cerebrovascular, and peripheral artery lesions; therefore, this review paper which described the relation between inflation time of balloon angioplasty and the prognostic outcomes, is worth reading. To enhance the quality of the paper, some points as mentioned below should be described much more in detail.

General Comments:

In general, this is a well-planned unique study and the protocol is presented in a clear manner. All sections are well written. We recommend addressing the following minor comments:

Abstract and Methods sessions

Please clarify whether drug-eluting and/or cutting balloons are included in this analysis. As well as, please provide the information whether in-stent restenosis lesions are included.

Background, Objectives, Discussion, List of Abbreviations.

No suggestions.

• Specify type of balloon (eg: drug coating, cutting, etc)
  o This is another valid point that has also been raised by other reviewers, and we will also stratify our analysis by device.

• Inclusion of treatment on restenosis
  o Other reviewers also identified concerns regarding the treatment of restenosis. We have specified and justified that we will only examine de-novo stenoses.