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**Manuscript NO:** 47098

**Title:** Neuraxial adjuvants for the prevention of perioperative shivering during cesarean section: a network meta-analysis following the PRISMA guidelines

**Dear editor,**

We sincerely thank you for handling the reviewing of our manuscript.

We appreciated the reviewer's time and effort in reviewing our manuscript, we are grateful for his/her professional comments and suggestions.

We have taken the comments on board to improve and clarify the manuscript. Please find below a detailed point-by-point response to the comments (reviewer's comments in black, our replies in blue).

Yours sincerely,

Qibiao Wu

June 25, 2019

#### **Response to reviewer**

1. I consider it important that the authors make the pairwise meta-analysis to directly compare the different neuraxial adjuvants. Why was there no comparison of the drugs between them, but only with placebo? The authors conclude that "neuraxial pethidine, fentanyl, dexmedetomidine, sufentanil are more efficacious than other medications in the prevention of shivering during caesarean section. Although pethidine is the most effective adjuvant for shivering prevention, it significantly increases the incidence of nausea and vomiting. Considering the risk-benefit profiles of the included neuraxial adjuvants, fentanyl is probably the optimal choice." However, the findings

are based on meta-analyzes comparing these drugs with placebo.

If it is possible to compare the neuraxial adjuvants between them, will the results regarding reduction of the outcomes considered be the same?

If neuraxial pethidine is compared with fentanyl, is the latter probably even the best choice?

**Response:** We agree with the reviewer that it is important to make the pairwise meta-analysis to directly compare the different neuraxial adjuvants. But, because the research meaterials for meta-analysis were published studies, after a comprehensive literature search, there were only six trials that directly compared different drugs (Table 1-1), and the compared drugs were different between trials, all the other 20 trials compared the drugs with placebo (Table 1-2). Many interventions (drugs) are available and few of them have been studied in head-to-head studies. This scenario precludes conclusions to be drawn from comparisons of all interventions profile, it was impossible for conducting a traditional (pairwise) meta-analysis to directly compare two neuraxial adjuvants (Figure 1), [1,2] but a network meta-analysis applies to this scenario because it allows the estimation of metrics for all possible comparisons in the same model, simultaneously gathering direct and indirect evidence (Figure 2).[1]

Only when two or more trials perform the same pairwise comparisons (directly compare same drugs), a pairwise meta-analysis will be possible. So far, there is no trial that directly compares neuraxial pethidine with fentanyl, therefore, currently it is impossible to perform a pairwise meta-analysis to evaluate whice one is the best choice (Figure 1). [1,2]

**Table 1-1   Characteristics of trials and patients**

First author, year	Size	Intervention
Han C 2014	60	Fentanyl vs. Dexmedetomidine vs. Placebo
Qi X 2016	118	Dexmedetomidine vs. Morphine vs. Placebo
Abdollahpour A 2015	75	Midazolam vs. Sufentani vs. Placebo
Hong JY 2005	120	Morphine vs. Pethidine vs. Placebo
Amit A 2016	60	Morphine vs. Fentanyl vs. Placebo

**Table 1-2 Characteristics of trials and patients**

<b>First author, year</b>	<b>Size</b>	<b>Intervention</b>
Palmer <i>et al</i> <sup>[15]</sup> , 1995	28	Fentanyl vs. Placebo
Shehabi Y 1990	62	Fentanyl vs. Placebo
Shami S 2016	150	Pethidine vs. Placebo
Techanivate A 2005	60	Fentanyl vs. Placebo
Roy JD 2004	40	Pethidine vs. Placebo
Chen X 2010	64	Sufentanil vs. Placebo
Bachmannmennenga B 2005	60	Sufentanil vs. Placebo
He L 2017	90	Dexmedetomidine vs. Placebo
Nasseri K 2017	50	Dexmedetomidine vs. Placebo
De FLG 2012	80	Sufentanil vs. Placebo
Rastegarian A 2013	100	Pethidine vs. Placebo
Khan ZH 2011	72	Pethidine vs. Placebo
Hanoura SE 2013	50	Dexmedetomidine vs. Placebo
Anaraki AN 2012	156	Pethidine vs. Placebo
Bajwa SJS 2012	100	Clonidine vs. Placebo
Bi YH 2017	60	Dexmedetomidine vs. Placebo
Yousef AA 2010	90	Magnesium sulfate vs. Placebo
Subedi A 2013	77	Tramadol vs. Fentanyl
Qian XW 2008	80	Sufentanil vs. Placebo
Reza FSH 2013	72	Magnesium sulfate vs. Placebo
Ali S 2011	80	Fentanyl vs. Placebo

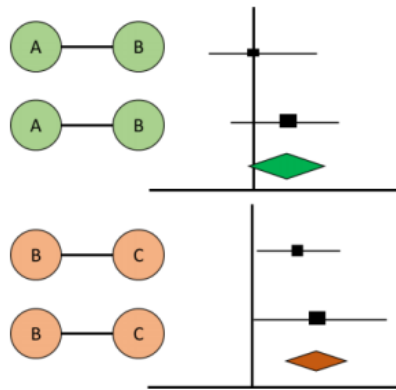


Figure 1. Example of pairwise meta-analyses.  
In the literature we can find RCT directly comparing interventions (e.g. A versus B in green; and B versus C in orange). Each RCT produce an effect in the meta-analyses (e.g. odds ratio, risk ratio, mean difference) represented by the lines in the graph and a global effect measure (diamond) that represents the reunion of the effects of the included studies. However, in this model is not possible to compare interventions A and C.

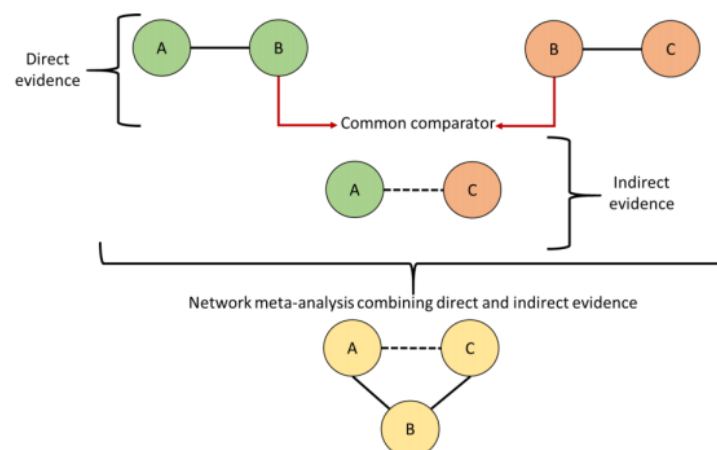


Figure 2. Direct and indirect evidence.  
In the literature we can find RCT directly comparing interventions (e.g. A versus B in green; and B versus C in orange). Each circle represents an intervention and lines represent direct comparisons. Dashed lines are for indirect comparison. An global effect value is generated for each comparison (direct or indirect). Indirect evidence is generated by using B as common comparator for the comparison of A versus C (model proposed by Bucher). Network meta-analysis combining both direct and indirect evidence may be built.

Figures cited from reference [1].

[1] Tonin FS, Rotta I, Mendes AM, Pontarolo R. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. *Pharm Pract (Granada)*. 2017 Jan-Mar;15(1):943. doi: 10.18549/PharmPract.2017.01.943. Epub 2017 Mar 15.

Ahn E, Kang H.

[2] Introduction to systematic review and meta-analysis. *Korean J Anesthesiol*. 2018 Apr;71(2):103-112. doi: 10.4097/kjae.2018.71.2.103. Epub 2018 Apr 2.

2. "Recent studies have shown that dexmedetomidine may be safe intrathecal supplement in Cesarean delivery." What studies? References? Page 16. "

**Response:** We have added references, as below,

Recent studies have shown that dexmedetomidine may be a safe intrathecal supplement in Cesarean delivery<sup>[7,22]</sup>.

3. Besides, as showed in SUCRA curve graph (Figure 4), the four largest SUCRA values were as follows: pethidine (83.9), fentanyl (75.1), dexmedetomidine (66.9) and sufentanil (53.3)." PAGE 10. Please, Include in the text that refers to the incidence of shivering.

**Response:** In individual trial, there was an incidence of shivering for the neuraxial adjuvant(s) studied, but network meta-analysis gathered direct and indirect evidence, the results of network meta-analysis didn't provide a specific shivering incidence for each neuraxial adjuvant. In this network meta-analysis, Odd ratio (OR), SUCRA (the surface under cumulative ranking curve) values were used to compare the differences between the effects of neuraxial adjuvants.