PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Oral Paracetamol versus Oral Ibuprofen for closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Neonates (<32 weeks): A Blinded Randomized Active Controlled Non-Inferiority Trial
AUTHORS	Sundaram, Venkataseshan; Kumar, Ashutosh; Yadav, Rahul; Oleti, Tejo; Murki, Srinivas; Krishnan, Arun; Sundaram, Mangalabharathi; Saini, Shiv; Dutta, Sourabh

VERSION 1 - REVIEW

REVIEWER	Yurttutan, Sadik Kahramanmaraş Sütçü İmam Üniversitesi/Yenidoğan Ünitesi Turkey Competing interests: There is not any conflict of interest
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	Well designed study, Normally, enteral preperations of paracetamol and ibuprofen not prepared for treatment of PDA. Especially in preterm infants, they are not tolerated high osmolarity preperations. You have to determine osmolarity of these drugs which are ibuprofen and paracetamol. These drugs have high osmolarity because of they are include saccarides. High osmolarity occasionaly leads intestinal hemorrage.So, You have determine osmolarity of these drugs. Then, when you are use, diluated them with adequate salin.

REVIEWER	Oncel, Mehmet Yekta İzmir Katip Çelebi University, Division of Neonatolog, Turkey Competing interests: None
REVIEW RETURNED	24-Jun-2017

GENERAL COMMENTS	Medical treatment of PDA to be an important problem associated with high morbidity in very low birth infants and of great interest to mostly neonatologist. Paracetamol medication for PDA is gaining more attention recently. I think that this protocol, which is written well, will be liked by many authors. I have some minor correction suggestions: 1) Study background and rationale section should be extended about paracetamol. I think it is necessary to mention the review and meta-analysis about paracetamol. Please cited this articles:

	- Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants. Cochrane Database Syst Rev. 2015; 3:CD010061. -Terrin G, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2016; 101(2):F127-36. 2) Whether this study should be assessed for neurodevelopmental outcomes or not. Please provide information. This article which is find below may be cited: Oncel MY, Eras Z, Uras N, Canpolat FE, Erdeve O, Oguz SS. Neurodevelopmental Outcomes of Preterm Infants Treated with Oral Paracetamol Versus Ibuprofen for Patent Ductus Arteriosus. Am J Perinatol. 2017 Apr 10. doi: 10.1055/s-0037-1601564. [Epub ahead of print] 3) Please indicate whether supporters (fund) of this work.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

a) Both paracetamol and ibuprofen are prepared with the help of the pharmacy department of the Institute. The standard oral preparations are diluted to concentrations of 10mg/ml for ibuprofen and 15mg/ml for paracetamol by addition of inert substances of low osmolality. Hence, we believe that the formulated preparation would not increase the osmolality further and hence is not being measured in the current protocol.

b) While administering through orogastric tube, 0.5 ml to 1 ml normal saline would be used to flush the tube to ensure complete delivery of the drug. This portion has been added to the protocol and has been highlighted

Reviewer 2:

a) Study background and rationale section has now been expanded and necessary changes have been made to include more recent articles on paracetamol. We have also cited the articles stated by the reviewer

b) Even though assessment of long term neurodevelopment in babies who received paracetamol is important, it has not been planned for the current trial. Including at this stage would not be feasible as the trial is already recruiting subjects in all three centres

c) This trial is not being funded by any organization