Author's response to reviews

Title: Evaluation Of Splanchnic Oximetry, Doppler Flow Velocimetry In The Superior Mesenteric Artery And Feeding Tolerance In Very Low Birth Weight IUGR And Non-IUGR Infants Receiving Bolus Versus Continuous Enteral Nutrition

Authors:

Valentina Bozzetti (vbozzetti@hotmail.com)
Giuseppe Paterlini (g.paterlini@hsgerardo.org)
Valeria Meroni (vale.meroni@gmail.com)
Paola De Lorenzo (paola.delorenzo@unimib.it)
Maria Grazia Valsecchi (grazia.valsecchi@unimib.it)
Diego Gazzolo (dgazzolo@hotmail.com)
Frank Van Bel (F.vanBel@umcutrecht.nl)
Gerard HA Visser (g.h.a.visser@umcutrecht.nl)
Paolo E Tagliabue (p.tagliabue@hsgerardo.org)

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

Thanks for your comments. Hereafter please find answers to your main questions.

ANSWERS TO MAJOR POINTS:

1. In our NICU we admit 70-80 VLBW infants per year, so we are able to enroll at least 20 VLBW infants that will take part to this trial.

2. Sample size calculations were based on baseline CSOR data under bolus feeding, taken from a recent paper by Dave V, et al. (see reference No. 23). We considered a wide variability range for the CSOR mean, and in the most extreme scenario, the standard deviation is two-fold the mean. This seems appropriate also in our hands, on the basis of pilot data. We could also consider enlarging sample size, but initial data suggest that this be unlikely, unless very few IUGR are enrolled.

3. Only two operators will perform the Doppler evaluation. The Doppler of superior mesenteric artery will be performed according to a standardized technique (the transducer will be placed on the mid-abdomen above the umbilicus, the SMA will be identified at its emergency from the aorta and sample volume will be placed a few millimeters from its origin. The evaluations and the measurements will be performed on 5 contiguous homogeneous waves). Moreover the same operator will perform the evaluations during the two randomized feeds for patients.
ANSWER TO MINOR POINTS:

4. We decide not to enroll infants with birth-weight less than 700 grams because we have concerns regarding the fragility of the skin of such small babies (NIRS probe should irritate the abdominal skin).

5. We will specify in our inclusion criteria that our policy is to not enroll infants already included in other trial (no trials are actually ongoing in our NICU).

6. Infants are defined as IUGR when the AC measurement deviate 10% or more from the expected from the individual projected curve of growth. This in agreement with the guidelines for the definition of intrauterine growth restriction published by the American College of Obstetricians and Gynaecologists (ACOG) (Mandruzzato et al. Intrauterine growth restriction (IUGR) *J Perinat Med* 36 (2008) 277-81)

7. The reference n.15 refers to a pilot study regarding regional tissue oxygenation of some other vascular beds than splanchnic. This study is not actually under review, but it concluded that further study is warranted.

8. We postulate that no carry-over and period effect operate in our study, since the randomized comparison relies on 2 successive feedings given in the same day and NIRS measurements are taken immediately pre- and post-feeding (i.e. at expected CSOR peak). Therefore, it is unlikely that the modality of the first randomized feeding (either bolus or continuous) will prolong its activity/efficacy so to impact on the NIRS at the second randomized feeding, neither by inducing a modification which is likely to persist beyond the peak, nor by modifying the underlying status of tissue oxygenation. However, the
order of the randomized feeding regimes become crucial for the secondary analyses on the time needed to reach full enteral feeding (FEF) and on the growth parameters at FEF. Infants randomized to Group A receive 1 feeding by bolus and then switch to continuous regimen until FEF achievement, while Group B starts with continuous and then receives bolus until FEF. So, comparing the 2 randomized groups at FEF, actually means to compare bolus vs. continuous on the long run. First, the actual extent of missing values will be evaluated. According to our pilot data, this may not be a worrying issue. Secondly, we will consider their nature (i.e. whether they are missing completely at random, or missing at random, etc.). We are aware that strategies for missing values have several pros and cons and, if needed, will consider the most appropriate approach on the basis of the extent and the nature of the problem.