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Ronald Lee Koretz

Early enteral nutrition in the ICU

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In a recent article published in *Intensive Care Medicine*, Doig et al. [1] describe a systematic review assessing the value of early enteral nutrition in the intensive care unit. The last paragraph of the paper begins "Meta-analysis conducted on the methodologically sound clinical trials identified by our systematic review of the literature revealed a statistically significant reduction in mortality and pneumonia attributable to the provision of standard EN within 24 h of injury."

"Methodologic soundness" was defined as trials that were free of major methodological flaws, namely pseudo-randomization (because of the loss of concealment of allocation) and >10% loss to follow-up. (Although the investigators also assessed the trials for any element of blinding, blinding itself did not appear to be a criterion for inclusion.) Six such trials (Chiarelli 1990, Chuntrasakul 1996, Kompan 1999, Pupelis 2001, Kompan 2004, Nguyen 2008) were identified and employed in the meta-analyses. Even for these reports, Doig et al. in the Validity appraisal of the Results section, acknowledged that it was unclear if allocation concealment was accomplished (in addition to noting that there was no instance where blinding was done). Hence, the methodologic soundness only depended on the single criterion of <10% loss to followup.

The situation is more problematic. In the Methods section of Chiarelli 1990 [2], it is stated that the 20 patients were "randomly assigned to one of two groups by the case-control method." That method is not explained. The term "case-control" usually refers to an observational (and retrospective) study, not a prospective randomized one. If this study was prospective, one possible meaning of "case-control" is that the patients were assigned alternately; if so, there would be no concealment of allocation. Given the description by Chiarelli et al. how can we be sure that this was a properly randomized trial?

The Pupelis 2001 trial is also problematic [3]. As Doig et al. noted, there was an earlier report of this trial [4]; in that report, 11 patients were in the enteral nutrition group and 18 in the control group. In the final report, there were 30 patients in each arm, meaning that, in the period following the preliminary report, 19 and 12 patients were enrolled into treatment and control groups. If this trial was randomized, a patient had a 50% chance of being assigned to either arm. The likelihood that at least 18 of 29 patients would be assigned to the same arm is about 26%. Similarly, the likelihood that no more than 11 of the next 31 would be assigned to the same arm is 14%. Thus, the probability of having these events occur back to back is $14 \times 26\%$, or $< 4\%$ (equivalent to a p value <0.04). There is concern that, at least for the second half of the trial, the randomization was somehow distorted. It may even be that this trial was not randomized at all.

There is a separate confounding factor in three of the other trials (Chuntrasakul 1996, Kompan 1999, Kompan 2004), namely a disproportionate use of parenteral nutrition. There is evidence that parenteral nutrition increases the risk of infections [5]. Both protocols by Kompan et al. [6, 7] called for parenteral nutrition to be given to the entire control group beginning on the first day. In the Chuntrasakul trial, parenteral nutrition supplementation was given to enteral nutrition recipients when the enteral intake was "insufficient"; the control patients received nutritional support by "conventional method" (not defined) [8]. Thus, in all three trials, the use of parenteral nutrition became a confounding issue.

The problem with the randomized trials in the entire enteral nutrition literature is the absence of methodologic soundness, resulting in high risks of bias. Trials with high risks of bias typically overestimate purported treatment benefits [9]. Claims to the contrary notwithstanding, the evidence cited by Doig et al. is not methodologically sound. As such, it is not capable of supporting the claim that enteral nutrition reduces mortality and pneumonia in the critically ill.

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R. L. Koretz (✉)
Department of Medicine,
Olive View-UCLA Medical Center,
14445 Olive View Drive, Sylmar,
CA 91342, USA
e-mail: rkoretz@msn.com
Tel.: +1-818-3643205
Fax: +1-818-3644573