Indian J Pediatr (February 2016) 83(2):99–100
DOI 10.1007/s12098-015-1996-8

EDITORIAL COMMENTARY

Exchange Transfusion in Severe Neonatal Sepsis: Is it Beneficial?

Deepak Chawla [1]

Received: 9 December 2015 / Accepted: 14 December 2015 / Published online: 9 January 2016

Systemic infections are one of commonest causes of neonatal deaths. Despite specific treatment with antibiotics, severe sepsis has a high case fatality rate [1]. Adjuvant therapies like intravenous immunoglobulins and granulocyte colony stimulating factors have been ineffective in improving the outcome [2, 3]. In such a scenario, clinicians often try drastic but unproven measures to save a rapidly deteriorating neonate with severe sepsis. Double volume exchange transfusion (DVET) is one such measure which can rapidly clear the circulating pool of bacterial endotoxins and pro-inflammatory cytokines. Efficacy of DVET in improving the outcome of neonates with severe sepsis has not been proven in a well-conducted randomized controlled trial. Aradhya et al. must be congratulated for attempting to fill this void [4]. In this study, neonates with severe sepsis, defined as presence of objective evidence of infection and end-organ failure were randomized to receive standard therapy alone or standard therapy with DVET. Primary outcome of the study was all-cause mortality within 14 d of enrolment. Although target combined sample size was 184, due to slow recruitment, the study was terminated after enrolling a total of 83 neonates. Authors concluded that there was a "trend towards" decrease in mortality (risk ratio: 0.79, 95 % CI: 0.45–1.3, $P=0.4$) in the DVET group and DVET is a safe procedure in severely sick and septic neonates. What should a reader make out of this study? Does this study provide evidence supporting the use of DVET in management of severe sepsis? Is it correct to report the results as a trend towards benefit of the intervention being tested? The results of the study need to be interpreted taking into account the following points.

As required number of subjects could not be enrolled, the study was underpowered to detect an effect size of pre-stated magnitude. "Trend towards significant benefit" conclusion may have been drawn from the assumption that if the target sample size would have been achieved chances of random error would have decreased, thus narrowing the confidence interval and achieving statistical significance. What are the chances that if the study would have been continued, a statistically significant benefit would have been achieved? In an empirical demonstration, Wood et al. prove that in studies with P value bordering significance, even with 100 % additional recruitment, the probability of obtaining non-significant result is nearly 50 % [5]. Latter probability is even higher in this study as P value ($P=0.4$) is farther from the point of significance. Further, it has been demonstrated that the trials which stop early tend to overestimate the effect size [6]. Therefore, it implies that either DVET has no beneficial effect or if there is any, it is likely to be of smaller magnitude than the point estimate provided by the study (21 % reduction in mortality). As the study was not powered to detect a clinically significant increase in side effects of DVET, it would also not be correct to conclude that DVET is a safe procedure in these hemodynamically labile neonates.

Confidence interval (CI) provides better interpretation of results obtained in a clinical trial. In this study, the 95 % CI limits indicate that true parameter value of effect of DVET on all-cause mortality lies somewhere in between 55 % reduction and 30 % increase. Within this confidence interval range, each point does not have equal probability of being a true parameter. As shown in the confidence interval function plot (Fig. 1), with given data the intervention is more likely to be associated with a beneficial effect (decrease in mortality) than a harmful effect (increase in mortality) [7, 8]. Still there remains a

✉ Deepak Chawla
drdeepakchawla@hotmail.com

[1] Department of Pediatrics, Government Medical College and Hospital, Chandigarh 160030, India

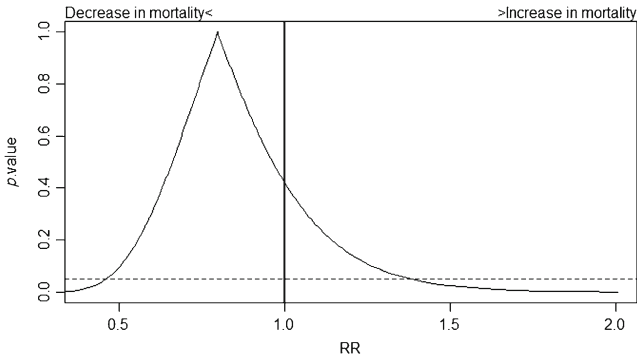

Fig. 1 Confidence interval (or *P* value) function plotted from results of the study. *Horizontal dashed line* intersects the curve at 95 % confidence interval (*P* value of 0.05) and *solid vertical line* represents the point of no effect

definite probability of harm with about one-fourth of the plot area on right side of the line of no effect.

Interpretations of the study results as stated above assumes that there is no bias in the study. Is there a possibility that the neonates in the DVET group were different from the neonates in the standard therapy group, thus moving the confidence interval function towards the line of no effect or *vice versa*? Baseline variables like birth weight, gestation and co-morbidities were comparable in the two groups. Illness severity as measured by Score for Neonatal Acute Physiology version II (SNAP II) was also comparable in the two groups. Randomized controlled design and equal distribution of baseline variables has minimized the possibility of selection bias in this study. However, sensitivity analysis done by authors does indicate a possibility of interaction between effect of DVET and degree of illness severity. Although the clinical team administering intervention and making decisions about co-interventions was not blinded, probability of performance bias was minimized by following standard treatment protocols and antibiotic policy.

Finally, it would be safe to conclude that current body of evidence does not support or refute the use of DVET in management of severe neonatal sepsis. Biological plausibility and higher probability of benefit than harm indicates need of a sufficiently powered and well-designed randomized controlled trial.

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding None.

References

1. Seale AC, Blencowe H, Zaidi A, et al. Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010. Pediatr Res. 2013;74:S73–85.
2. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database Syst Rev. 2013;7: CD001239.
3. Carr R, Modi N, Doré C. G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev. 2003;3:CD003066.
4. Aradhya AS, Sundaram V, Kumar P, Ganapathy SM, Jain A, Rawat A. Double volume exchange transfusion in severe neonatal sepsis. Indian J Pediatr. 2015. doi:10.1007/s12098-015-1841-0.
5. Wood J, Freemantle N, King M, Nazareth I. Trap of trends to statistical significance: likelihood of near significant P value becoming more significant with extra data. BMJ. 2014;348:g2215.
6. Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. BMJ. 2012;344:e3863.
7. Sullivan KM, Foster DA. Use of the confidence interval function. Epidemiol Camb Mass. 1990;1:39–42.
8. Nakazawa M. fmsb: Functions for Medical Statistics Book with some Demographic Data [Internet]. Available at: https://cran.r-project.org/web/packages/fmsb/index.html (2015). Accessed 9 Dec 2015.