Three vs Four Dose Schedule of Hepatitis-B Vaccine in HIV-infected Children

With respect to the recent publication by Jain, *et al*. [1] on the above topic, we seek the following clarifications:

Abstract mentions trial participants being fifty (25 per group) HIV-infected children aged 18 months - 12 years receiving ART for at least 6 months who had not received any prior dose of HBV vaccine, and were anti-HBs negative [1]. While in methods section it is mentioned as participants being seronegative for Hepatitis B virus (HBs antigen negative). Were participants anti-HBs antibody titre negative or HBsAg antigen negative? Or both antigen and antibody negative? Please clarify this confusion.

Regarding immunization status of participants, methods section mentions that immunization status was ascertained on the basis of previous immunization records [1]. Hepatitis B vaccination in immunization schedule of Delhi was introduced more than a decade ago [2]. So either participants were completely unvaccinated for all vaccines or vaccinated for all vaccines along with hepatitis B, depending on at what age they voluntarily stopped getting vaccines intentionally. So, no immunization record with no history of immunization too would have been a better proxy for unvaccinated subjects. How participants were left out for hepatitis B vaccine only? A previous randomized trial on similar topic [3] had subjects that were older, as routine hepatitis B vaccination had started just 1-2 years prior to the study.

Due to the convenience sampling, it is still unclear if double strength (20 µg) 4-dose schedule (0, 1, 2 and 6 months) is equally efficacious or superior to 3-dose schedule (0, 1 and 6 months), as the study was not powered to detect a difference unanswered thereby leaving this important question.

Baseline characteristics table shows mean age of groups I and II being 7 and 11 years, respectively [1]. It seems to differ significantly despite SNOSE technique and block randomization. Moreover, CONSORT flow chart shows 70 participants being eligible. While during enrollment, 40 (on summing up) were excluded.

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AUTHORS' REPLY

We thank the readers for their interest in our work [1] and provide the following clarifications: Regarding the inclusion criteria of participants, we wish to clarify that HIV-infected children aged 18 months - 12 years who had been receiving ART for at least 6 months and who had not received any prior dose of HBV vaccine were eligible, provided they were seronegative (HBs antigen negative). Immunization status for hepatitis B was assessed by studying the immunization cards of the child as well as absence of anti-HBs antibodies. We had noticed that the immunization records of some of these children were incomplete due to reasons like relocation/ migration, or where the parents had succumbed to HIV. Hence, relying solely on immunization records and history, did not seem a robust method.

Although, hepatitis B vaccination had been introduced in several Indian states almost a decade ago, the coverage of hepatitis B vaccine was reported low with huge gaps in coverage of DPT3 and HBV3 persisting [2]. A survey from India [3], reported that in 2015-16, 45% of the children aged 12-59 months were not fully vaccinated against hepatitis B, and 20% children had not received even a single dose of hepatitis B vaccine. Some of the participants in our study had been born in remote rural areas and had later migrated to Delhi, and therefore had not received hepatitis B vaccine. Some of these children had also not received other vaccines; the missing vaccination doses were administered by us during their visits to the anti-retroviral clinic.

The disparity in ages of participants in both groups despite block randomization may have been due to the small sample size and because we did not perform stratified randomization [4]. We excluded 20 children out of 70 eligible children. The CONSORT diagram depicts that 20 children were excluded and also elucidates the reasons for exclusion [1].

We agree that the research question addressed remains unanswered. Finding even 50 children who had never received any dose of hepatitis B vaccine was very challenging for us, and hence a convenience sampling was done. This question may be answered by pooling similar data from other studies and performing a meta-analysis.

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Intravenous Acetaminophen vs Intravenous Diclofenac in the Management of Painful Crisis in Sickle Cell Disease

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We appreciate Panda, et al. [1] for their work on efficacy of intravenous (IV) acetaminophen and diclofenac for the management of pain in patients with Sickle cell disease (SCD) vaso-occlusive crisis (VOC). However, we would like to comment on few aspects of this article.

i) In the Introduction section, authors have mentioned "*IV diclofenac is the current standard of care for management of skeletal VOCs in SCD*" [1] but the guidelines suggest the management of acute pain in sickle cell VOC is based on the severity of pain. In patients with mild to moderate pain, non-steroidal anti-inflammatory drugs (NSAIDS) can be used, unless contraindicated, whereas opioids are recommended as first line drugs in patients with severe pain [2].

ii) Authors have stated that oral NSAIDs are associated with gastric side effects [1]. The primary mechanism of gastritis by NSAIDs is by inhibition of prostaglandin production which is caused by both oral and parenteral NSAIDs [3]. Albeit less common, the risk of gastritis with parenteral NSAIDs cannot be ruled out.

iii) IV acetaminophen dose ranges from 10-15 mg/kg/dose and its effect lasts for 4-6 hours [4]. We fail to understand why paracetamol was given at 10 mg/kg/dose at 8-hour intervals.

iv) In the methodology section, authors have mentioned that patients who did not improve after home-based care and were symptomatic within 24 hours were included in this study. Many of these patients would have taken oral NSAIDs, particularly diclofenac, before reaching hospital. These patients should have been excluded from the study, as this could have an impact on the overall response rate.

v) In the result section, we found only 5 (4.91%) patients required add on therapy out of 102 patients included in this study, which signifies a remarkable response to both these drugs in acute crisis. Mean (SD) number doses required for complete relief of pain were 6 (4) and 8 (4) in the acetaminophen and diclofenac group, respectively. In our opinion patients who had more than 50% reduction in pain within 24 hours could have been switched over to oral drugs rather than prolonged parenteral therapy.

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AUTHORS' REPLY

i) We agree that opioids are still the standard of care for severe pain in SCD skeletal VOC, but IV diclofenac is the current standard of care for management of skeletal VOCs among HbSS children in our center, as opiates are not freely and continuously available, there is a lack of manpower to closely monitor respiratory depression in a high volume center, severe constipation with regular usage of opiates, more likelihood to develop opioid dependence in patients with severe and frequent VOCs, and gastric side effects with regular usage of oral NSAIDs. Moreover, we had observed that most patients coming to us with mild to moderate pain had already taken oral NSAIDs without relief.

Thus, due to non-availability of opioids, observed non-response to oral NSAIDs, and possibility of nephropathy with chronic diclofenac use, we planned this study.

ii) We agree with this statement.

iii) The dose range of IV paracetamol is 10-15 mg/kg/dose with duration varying from 4 to 8 hour, depending upon the situation. We enrolled only those patients who responded to 8-hourly regimen, for ease of analysis.

iv) We included only those patients who had not received any medications, and home- based care means only taking sufficient fluid and restricted outdoor activities to prevent dehydration.

v) We agree that patients who had more than 50% reduction in