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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

pain within 24 hours could have been switched over to oral drugs therapy and the same was also done by us. However, as our study end point was achieved, we have not mentioned these in our manuscript.

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Feeding Schedule in Preterm Infants: Two hourly versus Three Hourly

We read with interest the recently published randomized controlled trial by Yadav, et al. [1] comparing two-hourly and three-hourly feeding schedule in very-low-birth-weight neonates. We seek the following clarifications:

i) It is not clear whether the neonates were randomized at birth, at the time of introduction of feeds or at a specific time point within the first 96 hours. This is important, the time of randomization has a direct bearing on the primary outcome.

ii) The authors mention that the subgroup analysis was as per birthweight (1000-1250 grams vs >1250 grams), however, the same is not reported here. This subgroup analysis is vital and will help in increasing the generalizability in babies <1250 grams.

iii) In this trial, 40% of the enrolled neonates were small for gestational age (SGA) who are at higher risk for feed intolerance, hypoglycemia, and necrotizing enterocolitis (NEC) [2]. Therefore, it is desirable to have a subgroup analysis for SGA neonates for the above-said outcomes.

iv) What was the rationale for excluding infants with the absent or reversed end-diastolic flow? A recent large body of evidence did not show any interaction between antenatal absent or reversed end-diastolic umbilical flow and feeding advancement [3].

v) One of the major rationales of doing this trial was that three hourly feeding intervals might reduce nursing time in a resource-constrained setting. The previous study has shown that three hourly feedings are associated with shorter nursing time per infant [4]. It is desirable to have this data.

vi) Probiotic use can have a direct impact on mortality and NEC rates and may act as a confounder. Therefore, it is desirable to compare the probiotic use among two groups.

vii) Though the authors have presented time to full enteral feeds, many preterm neonates (<1250 grams) must be on tube feeds at the time of enrolment. It will be interesting to know whether there was any difference among the two groups in the time to reach full oral feeds (spoon/paladi/cup) and the duration of the transition in neonates who were on tube feeds at enrolment.

Recently a group of researchers advocated that the clinical trials should choose uniform outcome measures and report all clinically relevant outcomes for uniformity [5]. For trials related to feeding a set of important clinical outcomes shall also include weight gain (g/kg/d), time to regain birth weight, length of hospital stays, duration of parenteral nutrition, sepsis rates, along with other vital outcomes like retinopathy of prematurity and bronchopulmonary dysplasia. The authors should report this data to improve the generalizability of the study.

We sincerely believe that the clarification of the above points shall be immensely helpful for the clinicians and researchers.

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AUTHORS' REPLY

We appreciate the readers' interest in our study [1], and provide the clarifications:

i) The neonates were approached for randomization within first 96 hours and were enrolled as soon as the participants were deemed fit for inclusion. However, we did not record exact time of randomization or initiation of feeding.

ii) We agree with the point about subgroup analysis based upon weight and small for gestational age status. Detailed analysis shall be published later. There was no difference in time to reach full enteral feed, hypoglycemia, feed intolerance or necrotizing enterocolitis (NEC) among small for gestational age (SGA) neonates too (**Table I**). This finding is reassuring and indicates the applicability of