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On the difficulties of studying pain management in individuals with developmental delay

Dear Editor,

We were very interested to read the recent publication by Czarnecki et al[1] on the use of parent/nurse-controlled analgesia (PNCA) compared with PRN opioids for postsurgical pain management in children with developmental delay (DD), an important but often overlooked population. As the authors mention in their discussion, we have recently published on this subject and would like to correct a point they raise in relation to our publication, and to comment on study design and the interpretation of the available research evidence in this field.

Czarnecki et al[1] analysed data on 81 children with DD who had been randomised to one of three groups: PNCA with a basal infusion; PNCA without a basal infusion; or PRN opioids. They found that although patients receiving PNCA with a basal infusion consumed more opioid on average than the other two groups, there were no differences between the three groups on their primary outcome (pain score) or on the incidence of most side effects including respiratory depression. In their discussion they note that a shortcoming of their study was that the minimum sample size needed to detect a real difference in the primary

outcome would actually have been 180; the sample size for rare events, such as respiratory depression (RD), would have been greater still.

We recently investigated[2] whether children with neurodevelopmental disabilities (ND) including DD were more likely than children without such disabilities to experience RD while receiving morphine-NCA post-surgically—one of the most concerning side-effects of opioid administration as Czarnecki et al[1] point out. In our study,[2] a retrospective cohort design using prospectively collected data from 12,904 children who had received NCA, we found that the absolute rate of RD was very low (1.1% in the ND group) but that children with ND were about 1.7 times more likely to experience RD than other children. In addition, increased morphine consumption was associated with an increased risk of RD in the children with ND (whereas it was not in those without ND within the specified dose-range). In their discussion Czarnecki et al[1] state that we did not control for the presence of basal infusion in our study; in fact, we did enter this variable along with other elements of the analgesic regimen into our statistical models (the details of which are available with the article's on-line content) and found that the presence of basal infusion was not associated with an increased risk of RD, controlling for other factors including the on-demand bolus size and overall morphine dose.

Czarnecki et al[1] are to be congratulated on attempting this prospective randomised controlled trial (RCT) into what is undoubtedly a difficult medical problem and a difficult topic to study. RCT is frequently viewed as one of the most reliable methodologies and therefore among the highest levels of evidence when correctly conducted and interpreted. Although it is always disappointing when minimum recruitment targets are not met, the publication and careful

interpretation of such data still adds to the contemporary knowledge base and may contribute to future analyses. Czarnecki et al[1] found 'no difference' in side effects, including RD, between their three groups which might well have been expected given the small sample size and (thankfully) low incidence of this problem. Nevertheless this is in accordance with our data.

In the study of rare but potentially disastrous outcomes such as RD, high quality prospectively collected data from routine clinical and administrative datasets have distinct advantages when compared to studies employing *de novo* data collection, including: complete coverage of a population and consequently large sample sizes and statistical power; no selection bias, recruitment difficulties, participant drop-out or burden; contemporaneous data collection; and lower costs. Data can be linked from a variety of sources to enhance the richness of the dataset and the depth of analyses. That such studies are designed retrospectively does not detract from their utility or validity. As long as investigators ensure, as with all research, that the data are high quality and that the study design and analysis plan address chance, bias and confounding, such studies have the ability to provide answers to questions that would otherwise prove very difficult if not impossible to elucidate.

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Conflicts of interest

None to declare.