Perioperative care of neonates with Down’s syndrome: should it be different?

S. M. Walker
Portex Unit: Pain Research, UCL Institute of Child Health and Great Ormond Street Hospital NHS Trust, 30 Guilford St, London WC1N 1EH, UK
E-mail: suellen.walker@ucl.ac.uk

Assessment of pain intensity and provision of adequate analgesia are fundamental components of perioperative care for patients of all ages and all levels of cognitive ability. However, the very young, the developmentally delayed, or those with cognitive impairment may be at risk of under-treatment as assessment is more difficult in the absence of self-report or altered behavioural responses to pain, and/or provision of analgesia may be influenced by perceptions about the patient's sensitivity to pain or response to analgesia. Neonates and infants requiring surgery present additional challenges as the developing nervous system is especially vulnerable to alterations in sensory experience. Age-dependent changes in both the pharmacokinetic and pharmacodynamic profile of analgesics and anaesthetics can increase susceptibility to side-effects and limit the ability to extrapolate data from older patient populations. Specific evaluation of perioperative care in neonates with Down’s syndrome is warranted for several reasons: this condition is common (currently 1 in 740 live births in the UK), many have associated cardiac or duodenal anomalies that require surgery in early life, and there are limited data available to guide practice as patients with potential cognitive or neurological impairments are usually excluded from controlled analgesic trials. In addition, the phenotype of Down's syndrome is variable, both in terms of associated anomalies and in the degree of cognitive impairment, which ranges from mild (IQ: 50–70) to moderate and only occasionally to severe (IQ: 20–35). In this issue of the British Journal of Anaesthesia, Valkenburg and colleagues describe a retrospective case series of 45 neonates undergoing duodenal surgery, and concluded that pain scores and analgesic requirements did not differ in a subgroup of 15 patients with Down’s syndrome.

Perioperative analgesic requirements will be influenced by variability in both pain sensitivity and in analgesic efficacy. There is limited evidence for alterations in nociceptive processing in Down’s syndrome, with variable changes described in a rodent model (i.e. mild increased thermal withdrawal latency for the tail but not the hindpaw, and reduced behavioural response to formalin injection). Clinical studies are also currently inconclusive, as altered behavioural responses suggestive of either decreased or increased sensitivity have been reported in adults with Down’s syndrome. Either way, management of acute pain requires titration of an appropriate analgesic against individual response. Although opioid efficacy has not been widely evaluated in Down’s syndrome, morphine dose–response curves were not significantly altered in a mouse model, and data from the current series support the use of similar doses of perioperative morphine in neonates with or without Down’s syndrome.

Evaluation of pain and analgesic efficacy in neonates and infants is reliant on observer-based measurement, with well-established tools for use in pre-verbal children in different practice settings. As tools for assessment in intensive care are based on behavioural and physiological responses, they should be applicable to neonates with or without the potential for future cognitive impairment. The COMFORT-Behaviour scale assesses the intensity of six behavioural manifestations (alertness, calmness, facial tension, body movements, muscle tone, and respiratory response if children are ventilated or crying if they are spontaneously
Breathing), resulting in a score between 6 and 30, with >17 considered to be moderate-to-severe pain. This measurement tool has been validated for use in intensive care, and more recently has been reported to be reliable in children aged 0–3 yr with Down’s syndrome.12 Behavioural differences in neonates with Down’s syndrome influenced the cry, muscle tone, and facial response criteria within the COMFORT-B scale, but the degree of difference was small and felt not to be clinically significant. Facial response is a particularly important component of neonatal assessment, not only as a specific parameter in composite tools, but it is also likely to play a significant, although less explicit, role in observer-based numerical ratings of pain intensity. Facial actions have been rated as the most important indicators of pain in neonates at risk of neurological impairment13 but may be dampened or absent in some neonates.14,15 In adults, behavioural responses both at baseline and in response to an acute pain stimulus (immunization) varied with levels of cognitive impairment, and many with severe impairment had no facial response or ‘freezing’ which could be misinterpreted as insensitivity to pain.16 As repeated procedural interventions form a significant component of the pain experience of neonates in intensive care,17 prospective evaluation of the nature and sensitivity of change in facial response and other components of COMFORT-B to a defined acute stimulus such as heel lance would allow further evaluation of the sensitivity and specificity of this measure in children with Down’s syndrome. Similarly, evaluation of the response to immunizations during infancy and childhood would allow any age-related changes in both baseline behaviour, and in the response to a noxious stimulus, to be evaluated.

In addition to detecting whether pain is present or absent, a clinically useful tool must have sufficient sensitivity to grade the intensity of pain and evaluate the response to a pain management intervention. In the current series, all patients received continuous morphine infusion in neonatal intensive care unit (NICU) and had low pain scores on day 1 and scores of zero on day 2. As the authors note, the doses given may have been higher than required. Bolus doses of morphine were indicated for COMFORT-B scores ≥17 or numerical rating scale pain scores ≥4, but these occurred on only five occasions, and effects of bolus doses on pain scores are not reported. Additional studies will be required to evaluate the ability for measurement tools to effectively titrate analgesic administration against individual responses in neonates and infants with Down’s syndrome. This will be important not only for clinical trials evaluating the pharmacodynamic profile of analgesics, but also for clinical management of neonates on general wards where titrated bolus administration (i.e. nurse-controlled analgesia, NCA) is more frequently used than continuous infusions.2,18

When managing pain in neonates, both the behaviour of the neonate and also the behaviour of the observer may influence assessment and the subsequent provision of analgesia. The perceived risk of neurological impairment impacts on methods for assessing and managing procedural pain in NICU.19 Despite having the highest number of painful procedures, these neonates received fewer bolus doses of morphine, and there was no relationship between painful procedures and analgesic use.20 The actual or perceived risk of opioid-related side-effects can also influence analgesic administration. This is particularly relevant for children with Down’s syndrome, as many have associated cardiopulmonary anomalies. Overall, outcomes for children with Down’s syndrome are improving, but survival at 1 yr for those with other anomalies is significantly reduced.21 Approximately 50% of babies with Down’s syndrome have congenital heart disease, most commonly atrioventricular septal defects, but there is also a much higher incidence of persistent pulmonary hypertension of the newborn (PPHN; 5–13%).4 5 Structural respiratory anomalies (e.g. tracheal-gyomalacia, pulmonary hypoplasia), upper airway obstruction,22 and an increased risk of respiratory infections have also been reported.23 In a retrospective series of neonates undergoing duodenal surgery, the rate of early postoperative complications was higher in 86 children with Down’s syndrome compared with 141 without (45.3% vs 31.1%; P=0.03).24 However, the complication rate was even higher in subgroups with congenital heart disease, irrespective of whether they had Down’s syndrome or not. Similarly, the presence or absence of co-existing cardiorespiratory conditions is likely to have a greater impact on anaesthetic management than Down’s syndrome per se. In the current series,7 eight of the 15 neonates with Down’s syndrome had congenital heart disease, but it is not clear if this had any impact on analgesic administration. All patients were managed in an intensive care setting and were ventilated after operation, thus minimizing concerns regarding opioid-induced respiratory depression. A larger series will be required to determine if Down’s syndrome, the associated anomalies, or both increase the risk of opioid-related complications. However, rather than restricting the use of analgesia, such information should be used to inform the necessary level of monitoring and ward setting for postoperative care.

Randomized blinded controlled trials remain the gold standard for evidence-based medicine. However, recruitment of large homogeneous samples of neonates for analgesic trials is difficult. Although limited conclusions can be drawn from retrospective data in a relatively small sample, the work by Valkenburg and colleagues7 is an important first step, providing further support for the use of COMFORT-B for pain measurement and opioid administration for perioperative analgesia in neonates with Down’s syndrome requiring surgery and intensive care. Additional future information may be gained from translational laboratory studies in rodent models evaluating the impact ofthis chromosomal disorder on nociceptive processing and analgesic response at different developmental stages. Large case series or audit data can provide important information about the incidence of side-effects and complications.25 Additional observational studies evaluating the sensitivity and specificity of pain measurement tools for assessing both pain intensity...
and the response to analgesia are required for patients of all ages with Down’s syndrome. In clinical practice, irrespective of the patient’s current or future cognitive ability, pain management must continue to encompass not only measurements of pain intensity but also more global assessment (e.g. intercurrent conditions and general health, nature of the surgery, prior pain experience, current response to analgesia in terms of efficacy, and side-effects), in order to ensure individualized titration and optimization of pain interventions.

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