PAIN

Anaesthesia and postoperative analgesia in surgical neonates with or without Down’s syndrome: is it really different?

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Editor’s key points

- There is limited knowledge about the analgesic requirements of neonates with Down’s syndrome.
- This is a challenging patient group to study.
- This retrospective study looks at perioperative management and pain control using a validated scale.
- Neonates with Down’s syndrome did not appear to have different analgesic requirements.
- Despite sample size limitations, this study provides useful evidence for future work.

Background. Reports conflict on optimal postoperative analgesic treatment in children with intellectual disability. We retrospectively compared postoperative analgesics consumption between neonates with and without Down’s syndrome in relation to anaesthesia requirements and pain scores.

Methods. We analysed hypnotic and analgesic drug administration, pain scores [COMFORT-Behaviour (COMFORT-B) scale], and duration of mechanical ventilation during the first 48 h after surgical repair of congenital duodenal obstruction in neonates, between 1999 and 2011. Data of 15 children with Down’s syndrome were compared with data of 30 children without Down’s syndrome.

Results. General anaesthesia requirements did not differ. The median (inter-quartile range) maintenance dose of morphine during the first 24 h after operation was 9.5 (7.8–10.1) μg kg⁻¹ h⁻¹ in the Down’s syndrome group vs 7.7 (5.0–10.0) μg kg⁻¹ h⁻¹ in the control group (P=0.46). Morphine doses at postoperative day 2 and COMFORT-B scores at day 1 did not significantly differ between the two groups. COMFORT-B scores at day two were lower in children with Down’s syndrome (P=0.04). The duration of postoperative mechanical ventilation did not statistically differ between the two groups (P=0.89).

Conclusions. In this study, neonates with and without Down’s syndrome received adequate postoperative analgesia, as judged from comparable analgesic consumption and pain scores. We recommend prospective studies in children of different age groups with Down’s syndrome and in other groups of intellectually disabled children to provide further investigation of the hypothesis that intellectual disability predisposes to different analgesic requirements.

Keywords: anaesthesia, general; analgesia; Down syndrome; infant, newborn; intestinal atresia

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Methods

Participants and setting

After approval of the local ethics review board, we identified all patients who underwent surgical repair of congenital duodenal obstruction between March 1999 and February 2011 in Erasmus University Medical Centre—Sophia Children’s Hospital, Rotterdam, the Netherlands, and reviewed their medical records. The Erasmus MC Department of Paediatric Surgery and ICU serves as the only level III facility for those patients in a referral area comprising about 4 million inhabitants and 35 000 newborns yr⁻¹.

Eligible subjects were those who underwent surgical repair of congenital duodenal obstruction within the first 28 postnatal days. Exclusion criteria were: sedation or analgesic treatment during the 24 h before surgery, other surgical interventions at the same time or within 48 h after primary surgery for duodenal obstruction, or no digital record available.

Anaesthesia management

Anaesthesia management is not standardized in our centre and has changed over the years, reflecting new developments. Management of neonates with Down’s syndrome generally does not differ from neonates without Down’s syndrome, although, anaesthesiologists may anticipate possible airway management difficulties in neonates with Down’s syndrome. Atracurium was the preferred neuromuscular blocking agent until around 2008, when it was replaced with cisatracurium. Until 2008, most patients received barbiturates (thiopental or pentothal) as the hypnotic agent, which was then replaced with propofol. After 2008, a single-shot caudal block was used more frequently as anaesthesiologists became familiar with this technique. Evidence of specific anaesthesia for surgical repair of congenital duodenal obstruction is missing.

Postoperative pain protocol

A postoperative pain protocol has been in place since 1999 (Supplementary Fig. S1). The first step was regular pain assessment by an intensive care nurse; at least every 2 h during the first postoperative days and then every 8 h. The nurse used both the COMFORT-Behaviour (COMFORT-B) scale and the Numeric Rating Scale (NRS) for pain assessment.⁶⁻⁸ The COMFORT-B scale includes six items, each rated from 1 to 5. Adding the ratings for all six items provides a pain rating between 6 and 30. The COMFORT-B scale has been validated for use in children with and without Down’s syndrome.⁸⁻⁹ The NRS score for pain is a validated tool that asks a proxy (the nurse) to rate pain intensity (0, no pain at all; 10, worst imaginable pain). The NRS expresses the observer’s expert rating of the patient’s level of pain, taking the patients’ circumstances (disease-related, treatment related, and environmental- and patient-specific) into account.¹⁰ The NRS assessments—part of the pain management protocol since 1999—serve to differentiate between pain and distress. The second step of the protocol is analgesic therapy. At the end of surgery, neonates receive a loading dose of 100 μg kg⁻¹ morphine, followed by a maintenance dose of 10 μg kg⁻¹ h⁻¹. The protocol-associated decision-tree suggests that score combinations of COMFORT-B ≥17 and NRS ≥4 indicate moderate to severe pain, warranting opioid analgesia. Otherwise, maintenance doses of morphine are gradually decreased on the guidance of COMFORT-B and NRS scores. The pain management protocol makes no difference between children with or without Down’s syndrome. The sedation algorithm has been described previously.¹¹

In the study period, four children with Down’s syndrome and four without had been included in a randomized controlled trial about the potential morphine-sparing effects of rectal acetaminophen to continuous morphine infusions.¹² No differences in outcomes between the two treatment modes were seen; therefore, those neonates were not excluded from our study.

Measurements

The following patient characteristics were recorded: sex, gestational age at birth, post-natal age at the day of surgery, weight at the day of surgery, presence of trisomy 21 and diagnosis of associated congenital abnormalities (in particular, cardiac anomalies). We recorded amounts of anaesthetics, neuromuscular blocking agents, and analgesics (i.v. or caudal) given intraoperatively. From the surgeons’ report, we retrieved the cause of duodenal obstruction (duodenal atresia, duodenal web, or annular pancreas), duration of the surgery, and whether a central venous catheter had been placed. Furthermore, we recorded all hypnotics and analgesics administered during the first 48 h after operation and the duration of postoperative mechanical ventilation. Prospectively collected COMFORT-B scores and NRS ratings were retrieved from the Patient Data Management System (PDMS). Postoperative day 1 is defined as 0–24 h after surgery and postoperative day 2 as 24–48 h after surgery.

Statistical analysis

Data were analysed using SPSS version 19.0 (IBM, Chicago, IL, USA). The χ² test (or Fisher’s exact test in the case of low predicted cell counts) was used to compare nominal data for the neonates with and without Down’s syndrome. Continuous data are presented as median (inter-quartile range) and the two groups were compared using the Mann–Whitney U-test. The duration of morphine use is presented as mean (SD) and the two groups were compared using the t-test. All reported P-values are two-sided, and P-values of <0.05 are considered to indicate statistical significance.

Results

From 1999 to 2011, 107 children underwent surgical repair of congenital duodenal obstruction in our hospital. Figure 1 gives a flowchart showing that 45 were included in this study; that is 15 with Down’s syndrome (Down’s syndrome associated congenital abnormalities).
group) and 30 without (control group). The excluded neonates are listed in Figure 1.

Background characteristics of both groups are listed in Table 1. During surgery, a central venous catheter was placed in seven of the patients with Down’s syndrome vs 12 of the controls ($P = 0.67$). Children with Down’s syndrome had more often a congenital heart disease ($P = 0.001$), notably an atrioventricular septal defect. The causes of the congenital duodenal obstruction were comparable between the two groups.

General anaesthesia

General anaesthesia was induced i.v. in 14 (93%) of the children with Down’s syndrome, of whom three received a rapid sequence induction, while 24 (80%) of the controls, of whom 12 received a rapid sequence induction ($P = 1.00$).

The hypnotic agents administered during general anaesthesia are listed in Table 2. Five of the children with Down’s syndrome received a bolus of midazolam before transport to the intensive care unit (ICU) compared with one in the control group ($P = 0.01)$.

Fentanyl was administered to 14 (93%) of the children with Down’s syndrome and 26 (87%) of the controls. The median (IQR) dose was 6.7 (5–10) mg kg$^{-1}$ for the Down’s syndrome group vs 6.7 (4–10) mg kg$^{-1}$ for the control group ($P = 0.69$). The others (one with and four without Down’s syndrome) received sufentanil. Three of the patients with Down’s syndrome vs six of the controls received single-shot caudal analgesia during surgery ($P = 1.00$). Seven of these patients received 1–7 ml ropivacaine 0.2% and the other two patients 4 and 7 ml bupivacaine 0.25%.

Acetaminophen was administered intraoperatively as a loading dose in six (40%) of the patients with Down’s syndrome vs 13 (43%) of the controls ($P = 0.38$).
Postoperative intensive care treatment

Except one neonate in the control group, all patients received morphine after operation (Table 3). Continuous morphine administration was discontinued within the first 24 h in eight (53%) of the neonates with Down’s syndrome vs 13 (43%) of the controls (P=0.53). The mean (SD) total duration of morphine use was 28.2 (15.6) h in the Down’s syndrome group vs 31.9 (16.8) h in the control group (P=0.48).

Acetaminophen was administered after operation in 12 (80%) of the patients with Down’s syndrome vs 16 (53%) of the controls (P=0.08). Two patients with Down’s syndrome and three controls received midazolam after operation (P=1.00; Table 3).

Postoperative pain scores

Over the first two postoperative days, 429 COMFORT-B and 431 NRS scores had been recorded (Table 4). The median (IQR) COMFORT-B score after arrival at the ICU was 9 (8–11) in children with Down’s syndrome vs 10 (8–11) in controls (P=0.36). The median (IQR) COMFORT-B score at day 2 was 10 (9–11) in children with Down’s syndrome vs 11 (10–12) in controls (P=0.04). Almost all NRS scores were 3 or lower (low or no pain): 97% in the Down’s syndrome group vs 96% in the control group (P=0.43). Scores were 0 (no pain) in 110 (66%) observations in the Down’s syndrome group vs 217 (74%) in the control group (P=0.06). The combined scores suggested moderate to severe pain (NRS score of ≥4 combined with a COMFORT-B score of ≥17) only once in no more than two patients with Down’s syndrome and three controls.

Discussion

Our analysis did not reveal any substantial differences in anaesthesia and analgesia for congenital duodenal obstruction repair between neonates with and without Down’s syndrome, nor in pain scores. Even the duration of mechanical ventilation was not longer—as often expected—in the neonates with Down’s syndrome. Neonates with Down’s syndrome had a higher gestational age; this could explain their higher weight at surgery. However, it is unlikely that this influenced anaesthetic or postoperative management because medication was calculated per kilogram body weight. Congenital heart disease was more frequent in

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**Table 2** Intraoperative analgesics, hypnotics, and neuromuscular blocking agents, by group. *Fisher’s exact test. †χ² test. ‡Mann–Whitney test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Down’s syndrome (n=15)</th>
<th>Controls (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I.V., n (%)</td>
<td>11 (73)</td>
<td>12 (40)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Rapid sequence induction, n (%)</td>
<td>3 (20)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td>Inhalation, n (%)</td>
<td>1 (7)</td>
<td>6 (20)</td>
<td></td>
</tr>
<tr>
<td>Hypnotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates, n (%)</td>
<td>12 (80)</td>
<td>18 (60)</td>
<td>0.18†</td>
</tr>
<tr>
<td>Median (IQR) dose, mg kg⁻¹</td>
<td>4.7 (3.6–5.1)</td>
<td>4.6 (4.3–5.6)</td>
<td>0.63†</td>
</tr>
<tr>
<td>Propofol, n (%)</td>
<td>3 (20)</td>
<td>6 (20)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Median (IQR) dose, mg kg⁻¹</td>
<td>3.9 (3.6–3.9)</td>
<td>3.5 (2.4–7.3)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Sevoflurane, n (%)</td>
<td>5 (33)</td>
<td>5 (15)</td>
<td>0.20†</td>
</tr>
<tr>
<td>Isoflurane, n (%)</td>
<td>4 (27)</td>
<td>13 (43)</td>
<td>0.28†</td>
</tr>
<tr>
<td>Midazolam, n (%)</td>
<td>5 (33)</td>
<td>1 (3)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Median (IQR) dose, μg kg⁻¹</td>
<td>118 (55–419)</td>
<td>91</td>
<td>0.67‡</td>
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<tr>
<td>Neuromuscular blocking agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine, n (%)</td>
<td>3 (20)</td>
<td>13 (43)</td>
<td>0.12†</td>
</tr>
<tr>
<td>Median (IQR) dose, mg kg⁻¹</td>
<td>1.9 (1.4–1.9)</td>
<td>1.9 (1.6–2.2)</td>
<td>0.90‡</td>
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<tr>
<td>Atracurium, n (%)</td>
<td>10 (67)</td>
<td>11 (37)</td>
<td>0.06†</td>
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<tr>
<td>Median (IQR) dose, mg kg⁻¹</td>
<td>1.0 (0.5–1.3)</td>
<td>1.1 (0.8–1.4)</td>
<td>0.39‡</td>
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<td>Cisatracurium, n (%)</td>
<td>4 (27)</td>
<td>14 (47)</td>
<td>0.20†</td>
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<td>Median (IQR) dose, μg kg⁻¹</td>
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<td>170 (121–279)</td>
<td>0.80‡</td>
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<tr>
<td>Analgesics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl, n (%)</td>
<td>14 (93)</td>
<td>26 (87)</td>
<td>0.65*</td>
</tr>
<tr>
<td>Median (IQR) dose, μg kg⁻¹</td>
<td>6.7 (5.0–10.1)</td>
<td>6.7 (4.0–9.9)</td>
<td>0.69‡</td>
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<tr>
<td>Sufentanil, n (%)</td>
<td>1 (7)</td>
<td>4 (13)</td>
<td>0.65*</td>
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<td>Median (IQR) dose, μg kg⁻¹</td>
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<td>0.4 (0.3–0.6)</td>
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<td>Caudal block, n (%)</td>
<td>3 (20)</td>
<td>6 (20)</td>
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<td>Acetaminophen, n (%)</td>
<td>6 (40)</td>
<td>13 (43)</td>
<td>0.83‡</td>
</tr>
<tr>
<td>Median (IQR) dose, mg kg⁻¹</td>
<td>22 (8–28)</td>
<td>25 (8–35)</td>
<td>0.58‡</td>
</tr>
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</table>
neonates with Down's syndrome, which is consistent with findings from previous studies. Children with Down's syndrome received more often a bolus midazolam before transport to the ICU. COMFORT-B scores at day 2 were lower in children with Down's syndrome than in children without Down's syndrome, but the difference is clinically not significant.

The question arises whether our findings tally with those of previous studies. Table 5 provides an overview of previous studies and the present study. Valid comparison, however, is hampered by the different age groups and the heterogeneity of diagnoses and surgical procedures in the previous studies. Two reported that the intellectually disabled children received less intraoperative analgesia than the others. One reported more postoperative analgesia and one less postoperative analgesia in the intellectually disabled children. In addition, a questionnaire among physicians revealed that 89% agreed with the statement that intellectually disabled children receive subtherapeutic doses of analgesics.

Two of the previous studies also evaluated pain scores. One observed lower pain scores in the intellectually disabled children but lacked statistical testing. In the other, pain scores had been documented in only one-third of the children with cerebral palsy and these did not differ from those of the children without cerebral palsy. In view of the above, the question remains whether potential differences in pain experience, pain expression, or both of intellectually disabled children influence analgesic requirements (what they need) or pain management (what they get) in these children. The COMFORT-B scale has been validated by our group for the use in 0- to 3-yr-old children with Down's syndrome as well. Therefore, we have reason to believe that at this age, the pain expression of children with Down's syndrome is similar to other children. It does remain possible that neonates with Down's syndrome experience pain differently. Adults with Down's syndrome are reported to be more sensitive for heat pain. Since several pain-related genes (ADAMTS5, GRIK1, S100B, RUNX1, KCNE1, and KCNJ6) are located on chromosome 21, it will be important to study the effect of trisomy 21 on pain experience and the pharmacokinetics and pharmacodynamics of analgesics.

In the present study, the ICU's postoperative pain protocol provided for adequate treatment of potential pain and distress, as demonstrated by generally low COMFORT-B and NRS scores in all children. Results from a recent study by our group suggest that independent of the presence of Down's syndrome, neonates, in particular those younger than 10 days, have impaired pharmacokinetic capacity to metabolize morphine. This study provided new dosing recommendations based on a population pharmacokinetic model of i.v. morphine in children up to the age of 3 yr old. Simulations showed that a different dosing regimen would result in a more narrow range of morphine and metabolite concentrations. This new dosing recommendation for morphine entails a 50% reduction in children younger than 10 days old. Since most of the children in our study were younger than 10 days, the administered doses may therefore have been to the upside. As such, it might be speculated that...
Conclusions

In this study, both neonates with and without Down's syndrome received adequate postoperative analgesia, as judged from comparable analgesic consumption and pain scores. The pain scores were low and this finding suggests that these neonates, independent of the presence of Down's syndrome, might have been pain-free with less analgesia. Since evidence is still scarce and contradicting, we recommend prospective multicentre studies evaluating postoperative pain management in different age groups of children with Down's syndrome and in other groups of intellectually disabled children. These studies should preferably use a randomised controlled trial design comparing different analgesic regimens. In this way, conclusive evidence on the premise that intellectual disability predisposes to different analgesic requirements can be obtained.

The neonates in our analysis may have been pain-free with even less analgesia. A new pharmacodynamic study is needed to validate these new dosing recommendations, specifically also in intellectually disabled children.

Study limitations

Judging from the insignificant differences found between the two groups, the study could have been underpowered. For two important outcome parameters, we determined the sample size required to result in a statistically significant difference. First, the maintenance dose of morphine on day 1 was higher in children with Down’s syndrome; 76 patients in each group would be required to make this difference statistically significant. Secondly, 260 patients in each group would be required to make the difference in COMFORT-B scores at day 1 statistically significant. Given the incidence of congenital duodenal obstruction of 1.16–3.06 per 10,000 live births,5 such a study would be challenging, but may be usefully informed by the current work.

Complications and unexpected events were not registered during most years of our study period. Therefore, we are not able to present reliable data regarding complications or unexpected events.

Table 5 Comparison of the available evidence. *Analgesic doses compared with the control group. †The difference between the two groups has not been tested in the study by Malviya and colleagues. ‡Pain scores were available in only 31% of the study group

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study group</th>
<th>Control group</th>
<th>Type of surgery</th>
<th>Intraoperative analgesia of the study group*</th>
<th>Postoperative analgesia of the study group*</th>
<th>Pain scores in the study group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gokhal and colleagues6</td>
<td>Retrospective case–control study</td>
<td>16 children with Down’s syndrome (mean age: 5 yr)</td>
<td>16 children without Down’s syndrome (mean age: 5 yr)</td>
<td>Cardiac surgery</td>
<td>Not available</td>
<td>↑</td>
</tr>
<tr>
<td>Malviya and colleagues3</td>
<td>Retrospective cross-sectional study</td>
<td>19 intellectually disabled children (mean age: 11 yr)</td>
<td>23 children without intellectual disability (mean age: 11 yr)</td>
<td>Spinal fusion surgery</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>Koh and colleagues15</td>
<td>Prospective cohort study</td>
<td>152 intellectually disabled children (mean age: 10 yr)</td>
<td>148 children without intellectual disability (mean age: 8 yr)</td>
<td>Various</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Long and colleagues16</td>
<td>Retrospective cross-sectional study</td>
<td>71 children with cerebral palsy (29 of them were intellectually disabled) (mean age: 11 yr)</td>
<td>77 children without cerebral palsy (mean age: 11 yr)</td>
<td>Orthopedic surgery</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Present study</td>
<td>Retrospective cross-sectional study</td>
<td>15 children with Down’s syndrome (median age: 3 days)</td>
<td>30 children without Down’s syndrome (median age: 2 days)</td>
<td>Congenital duodenal obstruction repair</td>
<td>=</td>
<td>=</td>
</tr>
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</table>
Funding
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References
4 Gakhal B, Scott CS, MacNab AJ. Comparison of morphine requirements for sedation in Down’s syndrome and non-Down’s patients following paediatric cardiac surgery. Paediatr Anaesthesia 1998; 8: 229–33
7 van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 2000; 84: 367–77
21 Lacroix-Fralish ML, Ledoux JB, Mogil JS. The Pain Genes Database: an interactive web browser of pain-related transgenic knockout studies. Pain 2007; 131: 3.e1–4

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