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

A. J. Valkenburg[1,3]*, M. van Dijk[1,3], T. G. de Leeuw[2], C. J. Meeussen[1], C. A. Knibbe[4] and D. Tibboel[1,3]

[1] Department of Paediatric Surgery and [2] Department of Paediatric Anaesthesiology, Erasmus University Medical Centre—Sophia Children's Hospital, Dr Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands
[3] Pain Expertise Centre, Erasmus University Medical Centre, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[4] Department of Clinical Pharmacy, St Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, The Netherlands

* Corresponding author. E-mail: a.valkenburg@erasmusmc.nl

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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Research on systematic pain assessment and adequate analgesic therapy in children and neonates is on the rise.[1] It is not clear whether the 'standard' dosing regimens are applicable to intellectually disabled children,[2] although the evidence indicates potential differences in analgesic requirements for intellectually disabled children. Fewer children with intellectually disability were assessed for pain after spinal fusion surgery and they received smaller doses of opioids.[3] On the other hand, Gakhal and colleagues[4] found that children with Down's syndrome were more likely to receive morphine on day 3 after cardiac surgery than were controls.

Most studies in children with intellectual disability are limited by the sample heterogeneity in terms of aetiologies and intellectual disability levels. The reported incidence of congenital duodenal obstruction in children with Down's syndrome is 369 per 10 000 live births, far exceeding that in children without Down's syndrome, from 1.16 to 3.06 per 10 000 live births.[5] This makes repair of duodenal obstruction eminently suitable for comparison of anaesthesia, analgesia, and pain scores between a well-defined group of neonates likely to have future intellectual disability and a group of neonates with a lesser risk of future intellectual disability.

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 post-natal 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, anaesthetists 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 anaesthetists 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 $\mu g\ kg^{-1}$ morphine, followed by a maintenance dose of 10 $\mu g\ kg^{-1}\ h^{-1}$. 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 χ^2 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
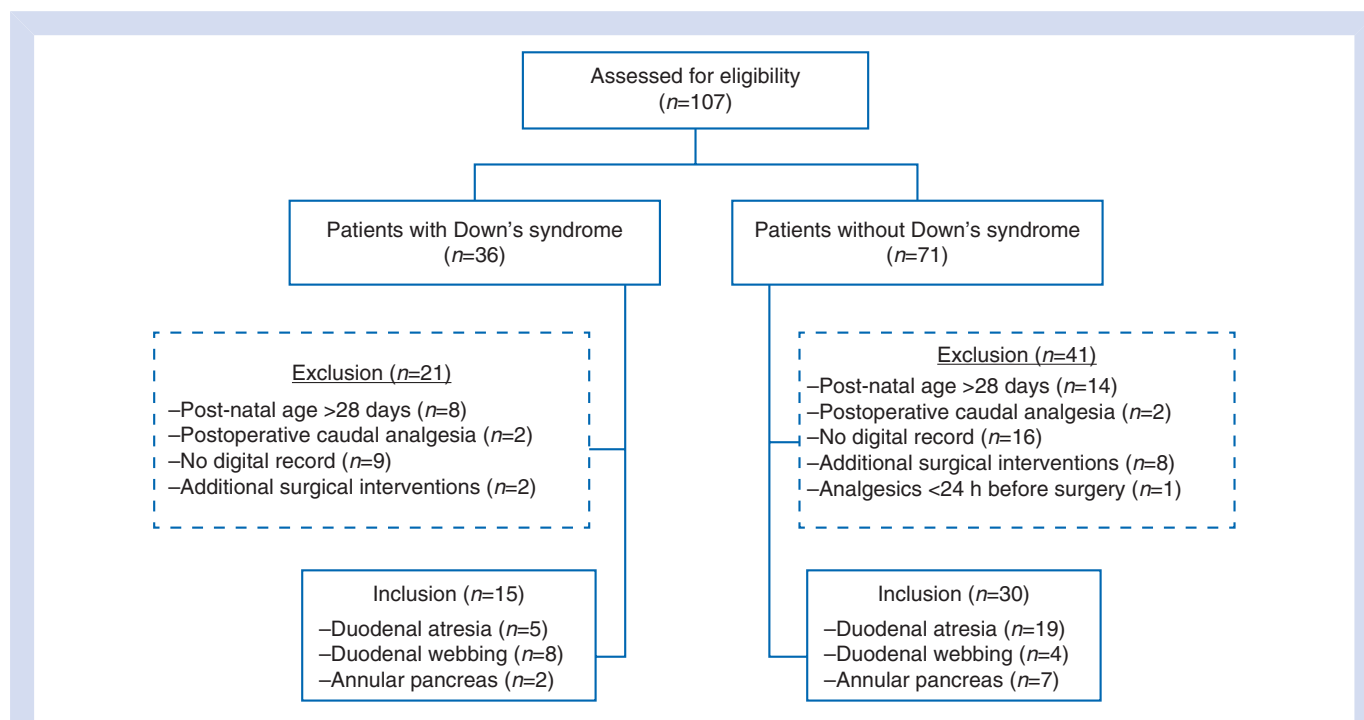
Fig 1 Flowchart for the 107 children assessed for eligibility.

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 were induced i.v., 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 children without Down's syndrome. The median (IQR) dose was 6.7 (5–10) μg kg^{-1} for the Down's syndrome group *vs* 6.7 (4–10) μg 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

Table 1 Patient characteristic, by study group. Data are expressed as median (IQR) or proportion. IQR, inter-quartile range. *P-value from χ^2 test. †P-value from Mann–Whitney U-test. ‡P-value from Fisher's exact test

Characteristic	Down's syndrome (n=15)	Controls (n=30)	P-value
Male/female, n	12/3	9/21	0.002*
Gestational age (weeks)	37 (36–40)	36 (33–38)	0.021†
Presence of congenital heart disease, n (%)	8 (53)	2 (7)	0.001‡
Age at surgery (days)	3 (1–10)	2 (1–4)	0.30†
Weight at surgery (kg)	2.8 (2.5–3.0)	2.2 (1.7–2.6)	0.005†
Duration of surgery (min)	187 (149–201)	167 (144–208)	0.78†
Postoperative ventilation, n (%)	12 (80)	25 (83)	1.00‡
Duration of postoperative ventilation (h)	32 (16–46)	27 (18–46)	0.89†

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).

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

Characteristic	Down's syndrome (n=15)	Controls (n=30)	P-value
Type of induction			
I.V., *n* (%)	11 (73)	12 (40)	
Rapid sequence induction, *n* (%)	3 (20)	12 (40)	0.06*
Inhalation, *n* (%)	1 (7)	6 (20)	
Hypnotics			
Barbiturates, *n* (%)	12 (80)	18 (60)	0.18†
Median (IQR) dose, mg kg^{-1}	4.7 (3.6–5.1)	4.6 (4.3–5.6)	0.63‡
Propofol, *n* (%)	3 (20)	6 (20)	1.00*
Median (IQR) dose, mg kg^{-1}	3.9 (3.6–3.9)	3.5 (2.4–7.3)	1.00‡
Sevoflurane, *n* (%)	5 (33)	5 (15)	0.20†
Isoflurane, *n* (%)	4 (27)	13 (43)	0.28†
Midazolam, *n* (%)	5 (33)	1 (3)	0.01*
Median (IQR) dose, µg kg^{-1}	118 (55–419)	91	0.67‡
Neuromuscular blocking agents			
Succinylcholine, *n* (%)	3 (20)	13 (43)	0.12†
Median (IQR) dose, mg kg^{-1}	1.9 (1.4–1.9)	1.9 (1.6–2.2)	0.90‡
Atracurium, *n* (%)	10 (67)	11 (37)	0.06†
Median (IQR) dose, mg kg^{-1}	1.0 (0.5–1.3)	1.1 (0.8–1.4)	0.39‡
Cisatracurium, *n* (%)	4 (27)	14 (47)	0.20†
Median (IQR) dose, µg kg^{-1}	197 (155–228)	170 (121–279)	0.80‡
Analgesics			
Fentanyl, *n* (%)	14 (93)	26 (87)	0.65*
Median (IQR) dose, µg kg^{-1}	6.7 (5.0–10.1)	6.7 (4.0–9.9)	0.69‡
Sufentanil, *n* (%)	1 (7)	4 (13)	0.65*
Median (IQR) dose, µg kg^{-1}	0.4	0.4 (0.3–0.6)	0.80‡
Caudal block, *n* (%)	3 (20)	6 (20)	1.00*
Acetaminophen, *n* (%)	6 (40)	13 (43)	0.83†
Median (IQR) dose, mg kg^{-1}	22 (8–28)	25 (8–35)	0.58‡

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

Table 3 Postoperative administration of analgesics and sedatives, by group. *Fisher's exact test. †Mann–Whitney U-test. ‡χ^2 test

Characteristic	Down's syndrome	Controls	P-value
Morphine			
Number of patients (%)	15 (100)	29 (97)	1.00*
Loading dose (μg kg^{-1})	100 (87–107)	107 (96–136)	0.09†
Maintenance dose day 1 (μg kg^{-1} h^{-1})	9.5 (7.8–10.1)	7.7 (5.0–10.0)	0.46†
Maintenance dose day 2 (μg kg^{-1} h^{-1})	7.0 (5.0–8.6)	5.0 (5.0–6.3)	0.47†
Acetaminophen			
Number of patients (%)	12 (80)	16 (53)	0.08‡
Median (IQR) cumulative dose day 1 (mg kg^{-1})	46 (29–78)	67 (45–88)	0.21†
Median (IQR) cumulative dose day 2 (mg kg^{-1})	72 (44–82)	59 (28–77)	0.61†
Midazolam			
Number of patients (%)	2 (13)	3 (10)	1.00*
Cumulative dose days 1 and 2 (μg kg^{-1})	398 (107–398)	703 (200–703)	0.40†

Table 4 Postoperative COMFORT-B and NRS* scores, by group. Data are expressed as median (IQR). *Numeric Rating Scale. †Two patients without Down's syndrome were not assessed due to a short stay on the PICU. ‡Mann–Whitney U-test

Characteristic	Down's syndrome ($n=15$)	Controls ($n=28$)†	P-value‡
Median number of scores per patient			
Day 1	6 (3–8)	4 (3–8)	0.30
Day 2	4 (3–6)	3 (3–7)	0.59
Median scores per patient			
COMFORT-B day 1	10 (9–11)	10 (9–11)	0.52
COMFORT-B day 2	10 (9–11)	11 (10–12)	0.04
Percentage of NRS scores of 0, i.e. no pain, per patient			
Day 1	86 (59–100)	75 (52–100)	0.65
Day 2	100 (59–100)	100 (69–100)	0.63

neonates with Down's syndrome, which is consistent with findings from previous studies.[5] [13] [14] 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[3] [4] [15] [16] 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.[17] Two of the previous studies also evaluated pain scores. One observed lower pain scores in the intellectually disabled children but lacked statistical testing.[3] 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.[16] In view of the above, the question remains whether potential differences in pain experience,[18] [19] 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.[9] 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.[20] Since several pain-related genes (ADAMTS5, GRIK1, S100B, RUNX1, KCNE1, and KCNJ6) are located on chromosome 21,[21] it will be important to study the effect of trisomy 21 on pain experience and the pharmacokinetics and pharmacodynamics of analgesics.[2]

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.[22] 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

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

	Study design	Study group	Control group	Type of surgery	Intraoperative analgesia of the study group*	Postoperative analgesia of the study group*	Pain scores in the study group
Gakhal and colleagues[4]	Retrospective case–control study	16 children with Down's syndrome (mean age: 5 yr)	16 children without Down's syndrome (mean age: 5 yr)	Cardiac surgery	Not available	↑	Not available
Malviya and colleagues[3]	Retrospective cross-sectional study	19 intellectually disabled children (mean age: 11 yr)	23 children without intellectual disability (mean age: 11 yr)	Spinal fusion surgery	=	→	↓†
Koh and colleagues[15]	Prospective cohort study	152 intellectually disabled children (mean age: 10 yr)	148 children without intellectual disability (mean age: 8 yr)	Various	→	=	Not available
Long and colleagues[16]	Retrospective cross-sectional study	71 children with cerebral palsy (29 of them were intellectually disabled) (mean age: 11 yr)	77 children without cerebral palsy (mean age: 11 yr)	Orthopedic surgery	→	=	=‡
Present study	Retrospective cross-sectional study	15 children with Down's syndrome (median age: 3 days)	30 children without Down' syndrome (median age: 2 days)	Congenital duodenal obstruction repair	=	=	=

the neonates in our analysis may have been pain-free with even less analgesia. A new pharmacodynamics 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 (α of 0.05 and β of 0.80). 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.

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 contradictory, 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 randomized controlled study design comparing different analgesic regimens. In this way, conclusive evidence on the premise that intellectual disability predisposes to different analgesic requirements can be obtained.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

None declared.

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References

1 Berde CB, Jaksic T, Lynn AM, Maxwell LG, Soriano SG, Tibboel D. Anesthesia and analgesia during and after surgery in neonates. *Clin Ther* 2005; **27**: 900–21

2 Valkenburg AJ, van Dijk M, de Klein A, van den Anker JN, Tibboel D. Pain management in intellectually disabled children: assessment, treatment, and translational research. *Dev Disabil Res Rev* 2010; **16**: 248–57

3 Malviya S, Voepel-Lewis T, Tait AR, et al. Pain management in children with and without cognitive impairment following spine fusion surgery. *Paediatr Anaesth* 2001; **11**: 453–8

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 Anaesth* 1998; **8**: 229–33

5 Cleves MA, Hobbs CA, Cleves PA, Tilford JM, Bird TM, Robbins JM. Congenital defects among liveborn infants with Down syndrome. *Birth Defects Res A Clin Mol Teratol* 2007; **79**: 657–63

6 van Dijk M, Peters JW, van Deventer P, Tibboel D. The COMFORT Behavior Scale: a tool for assessing pain and sedation in infants. *Am J Nurs* 2005; **105**: 33–6

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

8 Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT scale. *J Pediatr Psychol* 1992; **17**: 95–109

9 Valkenburg AJ, Boerlage AA, Ista E, Duivenvoorden HJ, Tibboel D, Van Dijk M. The COMFORT-behavior scale is useful to assess pain and distress in 0- to 3-year old children with Down's syndrome. *Pain* 2011; **152**: 2059–64

10 van Dijk M, Koot HM, Saad HH, Tibboel D, Passchier J. Observational visual analog scale in pediatric pain assessment: useful tool or good riddance? *Clin J Pain* 2002; **18**: 310–6

11 Ista E, de Hoog M, Tibboel D, van Dijk M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? *J Clin Nurs* 2009; **18**: 2511–20

12 van der Marel CD, Peters JW, Bouwmeester NJ, Jacqz-Aigrain E, van den Anker JN, Tibboel D. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *Br J Anaesth* 2007; **98**: 372–9

13 Dalla Vecchia LK, Grosfeld JL, West KW, Rescorla FJ, Scherer LR, Engum SA. Intestinal atresia and stenosis: a 25-year experience with 277 cases. *Arch Surg* 1998; **133**: 490–6

14 Singh MV, Richards C, Bowen JC. Does Down syndrome affect the outcome of congenital duodenal obstruction? *Pediatr Surg Int* 2004; **20**: 586–9

15 Koh JL, Fanurik D, Harrison RD, Schmitz ML, Norvell D. Analgesia following surgery in children with and without cognitive impairment. *Pain* 2004; **111**: 239–44

16 Long LS, Ved S, Koh JL. Intraoperative opioid dosing in children with and without cerebral palsy. *Paediatr Anaesth* 2009; **19**: 513–20

17 Malviya S, Voepel-Lewis T, Merkel S, Tait A. Difficult pain assessment and lack of clinician knowledge are ongoing barriers to effective pain management in children with cognitive impairment. *Acute Pain* 2005; **7**: 27–32

18 Lind J, Vuorenkoski V, Rosberg G, Partanen TJ, Wasz-Hockert O. Spectrographic analysis of vocal response to pain stimuli in infants with Down's syndrome. *Dev Med Child Neurol* 1970; **12**: 478–86

19 Hennequin M, Morin C, Feine JS. Pain expression and stimulus localisation in individuals with Down's syndrome. *Lancet* 2000; **356**: 1882–7

20 Defrin R, Pick CG, Peretz C, Carmeli E. A quantitative somatosensory testing of pain threshold in individuals with mental retardation. *Pain* 2004; **108**: 58–66

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

22 Knibbe CA, Krekels EH, van den Anker JN, et al. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. *Clin Pharmacokinet* 2009; **48**: 371–85