Higher risk of opioid-induced respiratory depression in children with neurodevelopmental disability: a retrospective cohort study of 12,904 patients

Running title: Morphine and neurodevelopmental disability

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Abstract

Background

Children with neurodevelopmental disabilities (ND) may be at risk of opioid induced respiratory depression (OIRD). We aimed to quantify the risks & effectiveness of morphine-NCA for postoperative pain in children with ND.

Methods

A retrospective cohort study of 12,904 postoperative children who received intravenous morphine-NCA. Subjects were divided into neurodevelopmental disability (NDG) and control groups (CG). Rates of clinical satisfaction, respiratory depression (RD) and serious adverse events (SAE) were obtained and statistical analysis including multilevel logistic regression using Bayesian inference was performed.

Results

2,390 of 12,904 patients (19%) had ND. There were 88 cases of RD and 52 SAEs; there were no opioid-related deaths. The cumulative incidence of RD in the NDG was 1.09% *vs* 0.59% in the CG, OR 1.8 (98% chance that the true odds ratio was >1). A significant interaction between postoperative morphine dose and ND was observed, with higher risk of RD with increasing dose. Satisfaction with morphine-NCA was very high overall, although children with ND were 1% more likely to have infusions rated as fair or poor (3.3% *vs* 2.1%, χ^2 $p<0.001$).

Conclusions

Children with ND were 1.8 times more likely to suffer RD, absolute risk difference 0.5%; OIRD in this group may relate to increased sensitivity to dose-related effects of morphine. Morphine-NCA as described was a safe & acceptable technique for children with ND & controls, but further evaluation of the effects of opioids in this vulnerable group are indicated.

Keywords

Morphine; Developmental Disabilities; Pain, Postoperative

Word count: 237

Introduction

Intravenous opioids are frequently used for the management of severe postoperative pain in children and are generally considered to have an acceptable safety profile.[1-4] However, some patient groups may be at increased risk of opioid-induced respiratory depression (OIRD), a potentially life-threatening side-effect.[5] Neonates, especially premature neonates, children with obstructive sleep apnoea (OSA), or renal impairment (RI), are thought to be at higher risk of OIRD; it is therefore important to identify such patients and institute appropriate monitoring if opioids are to be used with optimum safety.[2-5]

Children with neurodevelopmental disabilities (ND) are a large and important group in whom the challenges of effective and safe pain management are recognised. Communication difficulties, physical and physiological impairments, pharmacokinetic-pharmacodynamic differences and drug interactions add to the complexity of pain management in this group and may contribute to the suggestion that they are more susceptible to OIRD; however few data are available.[3, 6-16] High frequency of pain in children with ND and their increased likelihood to undergo surgery,[7, 17] shows a clear need for better understanding of analgesic effects in these vulnerable young people.[7,21]

We aimed to quantify the risks of respiratory depression (RD), serious adverse events (SAE), and rates of satisfaction in a group of morphine-treated postoperative children with ND. We hypothesised that children with ND would have a higher risk of both RD and SAE. We have previously described the use of morphine-NCA in our institution, including some of the data presented here, although previous studies did not address the current hypothesis, and a greater number of patients are included here.[2, 18]

Methods

Nurse-controlled analgesia

Morphine-NCA is an intravenous morphine infusion using a locked, programmable infusion pump, with the option for additional doses ('boluses') of morphine administered on demand by nursing staff, subject to a lockout period. The NCA protocol is given in Appendix 1.[2, 18] Patients receiving morphine-NCA are observed at least hourly during treatment. Pain scores were measured with the Wong-Baker Faces Rating Scale,[19] a 0-10 Numerical Rating Scale,[20] FLACC,[21] revised-FLACC,[22] COMFORT[23] or PAT[24] as appropriate and as these tools became available. Sedation was measured using the University of Michigan Sedation Scale.[25] Trained nurses are permitted to deliver bolus doses following pain assessment with the aim of maintaining pain scores below 4/10 on a numerical rating scale. Simple analgesics, paracetamol & NSAID, are prescribed (unless contra-indicated) for all patients and administered as appropriate. The administration of supplementary opioid analgesia is prohibited during NCA. Naloxone 4 μg kg^{-1} is prescribed *pro re nata* (as needed) for administration in the event of clinically significant RD at the discretion of clinical staff. Parents and other non-professional carers are not permitted to deliver morphine bolus doses.

Outcomes

Principal outcomes were: cumulative incidence of RD; cumulative incidence of SAEs; and satisfaction with analgesia. RD was defined as depression of respiratory rate below that stipulated by the NCA prescriber (a mandatory part of the NCA prescription) as judged and documented by the patient's clinical care team. SAEs were defined as in European Directive 2001/20 on good clinical practice in clinical trials as any untoward medical occurrence that results in death, is life-threatening, requires prolongation of existing hospitalization or results in persistent or significant disability or incapacity.[26] We deemed all instances of naloxone

administration for RD as SAE. Satisfaction was recorded at the end of treatment as very good, good, fair or poor according to assessments made by trained and experienced Clinical Nurse Specialists taking into account the opinions of other clinical staff, the family, and where possible, the patient.

Patients and data

We identified all patients aged 0-18 years who received intravenous morphine-NCA following major surgery at Great Ormond Street Children's Hospital, between 1996 and 2011. Prospectively documented data were collected at least once daily by trained and experienced Clinical Nurse Specialists and entered into a pain management case record at the bedside which was transcribed, when treatment was completed, to a secure electronic database. The database was maintained by trained staff and regularly reviewed; anomalous data being independently verified against original hospital records at point of entry.[2] Following extraction, data were re-checked for quality and consistency using standard graphical and statistical techniques. Institutional registration and approval were obtained according to local policies, (Project 1879, Great Ormond Street Hospital Clinical Audit Registration, February 2016) and data were processed in accordance with UK information governance requirements.

Patients who received morphine-NCA were identified as having ND from the clinical case record and divided into two groups: those with ND (NDG) and those without (control group, CG). Children were included in the NDG if the 'developmental delay' checkbox was completed on the case record and/or the clinical diagnosis included medical conditions known to cause neurodevelopmental delay, and evidence that the presence of neurodevelopmental delay had been confirmed on physical examination. Where possible, the

NDG was also sub-divided into groups by diagnosis (On-line Table 1). Data were also collected on known and theoretical confounders: age; weight; sex; RI; obstructive sleep apnoea (OSA); operation duration (minutes); type of surgery (grouped as cardiothoracic, general, urological, head and neck, neurosurgery, orthopaedic and plastics); administration of intraoperative opioids and dose; postoperative ward location (ward); length of NCA infusion (hours); whether the patient was initially commenced on a background infusion and infusion rate; initial NCA bolus size; and overall postoperative morphine dose (expressed in $\mu g\ kg^{-1}\ hr^{-1}$). The day of surgery is labelled day zero (D0) and is the time between infusion start and midnight; subsequent calendar days are labelled day one (D1), etc., until termination of the NCA infusion.

Statistical analysis

A summary of the statistical methods is given here; see the On-line Statistical Appendix for full details. Descriptive statistics were computed as median (IQR) and n (%). Possible effect modifiers were investigated using stratification. Expectation-maximization with bootstrapping using the R package *Amelia II*[27] was performed to impute missing values with ten imputed datasets. Multilevel logistic regression was used to analyse the incidence of RD and SAEs, allowing the intercept to vary by ward. Parameters were estimated using Bayesian inference from Markov chain Monte Carlo simulations with Gibbs sampling (see On-line Statistical Appendix for details on handling of missing data and Bayesian set-up). Model fit was assessed by examining the deviance information criterion (DIC) of each model: lower values of the DIC represent better fit; 5 units change indicates some substantial improvement and 10 units change definite improvement. As any increase in the risk of RD or SAE was considered clinically important, we calculated the probability that the true OR for ND was >1

in each model by computing the area under the curve of the posterior distribution which represented an OR >1.

Satisfaction was dichotomised into ‘Good or Very Good’, and ‘Poor or Fair’, and tested in complete case analysis (296 [2.3%] missing satisfaction values were missing) using χ^2 (Yates’ correction) or Fisher’s Exact as appropriate.

Analysis was conducted in the statistical computing environment R (Vienna, Austria: R Foundation for Statistical Computing, 2013) and WinBUGS (Cambridge, UK: Medical Research Council Biostatistics Unit, 2003). Data were obtained and analysed on all available patients.

Results

Patient demographics and morphine dose

Twelve thousand, nine hundred and four patients were included; the prevalence of ND was 19% (n=2,390). There were missing data on the following variables: operation duration (n=1,037, 8.0%), intraoperative opioid administration (n=958, 7.4%), infusion background, background rate and bolus size (n=44, 0.3% on all three) and overall postoperative morphine dose (n=148, 1.1%). Patient characteristics, operation duration and duration of morphine-NCA are shown in Table 1 (surgical categories broken down by group are given in On-line Table 2). Patients in the NDG were older and heavier (older patients in the control group are usually commenced on patient-controlled analgesia), were more likely to have OSA and had longer operation and postoperative NCA infusion durations (though these were not significantly different to the CG in all subgroups of ND).

Median postoperative morphine dose in the NDG was 16.31 μg kg^{-1} hr^{-1} on D0, compared to 15.02 μg kg^{-1} hr^{-1} in the CG (Table 2). As expected, morphine dose declined with each consecutive postoperative day in all groups. Actual values for all opioid doses are given in the on-line supplementary materials and were included in the overall analysis.

Respiratory depression

There were 88 cases of RD; 26 were in the NDG (cumulative incidence: 1.09%) and 62 were in the CG (cumulative incidence: 0.59%, Table 3). Further comparison by NDG diagnostic subgroup suggested that patients with Cerebral Palsy, Down's syndrome and encephalopathy appear to be most at risk of RD (1.68%, 1.84% and 2.53% *vs.* 0.59%, Table 3). About half of the incidents of RD occurred on D0 and 92% occurred within the first 48 hours (On-line

Table 7); the pattern was similar in both the NDG and CG. The distribution of RD among the covariates and stratified by NDG/CG is given in On-line Tables 8 and 9.

Figure 1A shows the posterior distribution of the effect of neurodevelopmental disability on the odds of RD in an unadjusted model. It shows that the odds of RD were 65% (OR 1.65, 95% CrI 1.03 to 2.63) higher in children in the NDG compared to those in the CG. There was a 98% chance that the true OR was >1.

Further models were constructed and the results did not appreciably change; details of these models can be found in On-line Table 10 and the respective posterior distributions for the effect of ND can be found in On-line Figure 1. In summary, in model 3, the effect of ND was augmented to OR 1.79 (1.05 to 3.04) after adjusting for age (age being a very important predictor in all models with older patients having a much lower risk of RD than neonates). Gender, presence of RI and OSA were not significant. Surgical category was entered in model 4 and this attenuated the effect size slightly but surgery was not significant, did not improve model fit and so was discarded. In model 5, the administration of intraoperative opioids, commencement on a background infusion, NCA bolus size and overall postoperative morphine dose on D0 were all not significant predictors of RD. Similarly, in model 6, there was no evidence of a time effect with year of surgery being insignificant.

A morphine-ND interaction term was entered and was significant (model 7). This is illustrated in Figure 2A, which indicates that the risk of RD in patients in the NDG rose with increasing postoperative doses of morphine within a therapeutic range, whereas this did not occur in the CG. This model had the best fit of all seven (lowest DIC).

The ward intercept SD in the model with no predictors (model 1) showed a degree of variability in the odds of RD by ward, which ranged from 0.001 to 0.023. About 62% of this variability was due to differences in ages and surgical categories of the patients seen on each ward; the remaining variability was not accounted for by the other measured variables.

Serious adverse events

There were 52 SAEs. Forty nine SAEs were RD treated with naloxone; 3 were judged not opioid related. Fourteen SAEs (0.59%) occurred in the NDG *vs* 38 (0.36%) in the CG (absolute risk difference 0.23%). Half of the SAEs occurred on D0 and 92% within the first 48 hours in both the NDG and CG (On-line Table 7).

The posterior distribution for the OR of ND in the unadjusted SAE model is given in Figure 1B which shows that those with ND were 1.42 times more likely to experience an SAE, though as the 95% CrI crossed 1 (0.77, 2.63) this finding was interpreted as non-significant. Results did not change appreciably in further models (On-line Table 11 and On-line Figure 1). Age was an important risk factor (as with RD) and none of gender, RI, surgical category, intraoperative and postoperative opioid administration or year was significant (models 3 to 6). There was a shallow interaction between postoperative morphine and ND (model 7) as shown in Figure 2B; this model had the best fit. The degree of variability in the risk of SAE due to ward was similar to that for RD.

Satisfaction

Overall, satisfaction was very good or good in 12,320 (98%) cases and fair or poor in 288 (2%). Morphine-NCA in the NDG was 1.2% more likely to be rated fair or poor than in the CG (3.3% *vs* 2.1%, χ^2 $p<0.001$). For the ND subgroups, fair or poor ratings patients in the

Cerebral Palsy group 26 (5.5%, $p<0.001$) and Developmental Delay 41 (2.9%, $p=0.032$), were also significant.

Discussion

This is the first large scale study specifically attempting to quantify, examine and better understand the risks of OIRD in children with ND. We compared 2,390 children with ND to 10,514 without, who were receiving morphine after major surgery and have found that the presence of ND, after correcting for confounders, was associated with greater risk of experiencing RD: a significant interaction between ND and postoperative morphine dose was also found. Although RD was more prevalent in the ND group, in the present study there appeared to be little or no difference in the risk of experiencing SAE, which is reassuring.

Neurodevelopmental disabilities are a group of congenital or acquired long-term conditions that are attributed to impairment of the brain and/or neuromuscular system and create functional limitations. Although easily identified clinically, they comprise a heterogeneous group where a specific diagnosis is not always ascribed. Such conditions may or may not be progressive, occur alone or in combination and in a broad range of severity and complexity. Their impact may include difficulties with movement, cognition, hearing and vision, communication, emotion, and behaviour.[28] Children with ND represent a significant proportion of children undergoing surgery and therefore postoperative pain, and in fact have been considered to be at increased risk of experiencing all types of pain.[17, 29-32] Despite this, few data are available to guide management and in fact they are often specifically excluded from research studies, and have been estimated to be represented in only 0.03% of the pain literature.[33, 34]

Respiratory depression is often considered to be a predictable side-effect of opioid analgesia; but it is the possible progression to cardio-respiratory collapse that could lead to serious permanent harm, or even death, that has been identified as the greatest safety concern for

clinicians.[5, 35] Fortunately, awareness of this potential, the recognition of 'at risk' patient groups and provision of appropriate monitoring has likely contributed to the low reported rates of serious harm; although there is concern that such low rates, the lack of a generally accepted definition of RD, methodological problems in undertaking multi-site population studies, under-reporting of individual cases, and the small size of many studies in children, may underestimate the true incidence of both respiratory depression and serious complications.[35] In the present single-centre study, we found the overall rates of RD to be reassuringly low (0.59-1.09%) but nevertheless slightly above the range of estimates from previous multi-site studies.[36] In strong agreement with previous studies patient age was the most consistent and important predictor of RD in all patients in the present study. The finding here that the generally accepted risk factors OSA and RI did not predict RD may imply that such risks can be successfully attenuated, a concept further supported by the low rate of progression to SAE that was observed in all groups.

Aside from the increased risk of RD in children with ND we also observed an increased 'sensitivity' to morphine in the NDG: i.e. patients with ND appeared to be more likely to experience RD with increasing morphine dose. The reasons for this are unclear but children with ND may have impaired respiratory drive, cardiorespiratory deficits, neuromuscular and postural abnormalities, gastro-oesophageal reflux, and are more likely to be treated with anti-epileptics, muscle relaxants, sedatives, and other medicines that were not controlled for in this study.[7, 11]

Whilst providing some data on the incidence and risks of OIRD in patients with ND, previous studies have been difficult to interpret owing to differences in study design, patient population, opioid drug, route, dosing and dosing frequency, monitoring practices, reporting

criteria and the lack of control groups.[3, 9, 15, 16, 37, 38] A small retrospective cohort study by Long, Ved and Koh found no differences in the risk of 'clinically significant oxygen desaturation' ($SpO_2 \leq 94\%$) between a group of children with (n=71) and without (n=77) cerebral palsy in the post-anesthesia care unit[9] whereas Chidambaran and others' case-control study, analysing 38 cases of naloxone administration to inpatients in a tertiary children's hospital reported risk factors <1 year, prematurity, OSA, obesity, underweight, and developmental delay.[16]

How profound and what type of ND might greater predispose to RD is not known. In the current study, children with cerebral palsy (non-progressive ND due to perinatal causes), Down's syndrome and encephalopathy appear to be at relatively greatest risk of developing both RD and SAE. Adverse peri-natal events are known to influence subsequent development of respiratory control and so further study of the underlying mechanisms might lead to important clues as to potential causation.[39] However, as firm conclusions regarding relative risks in sub-groups were difficult in this study as numbers were too low to perform multivariable analysis, further clinical study would also be required.

Strengths and limitations

While our study was conducted retrospectively using routine clinical data, those data were collected prospectively according to a mandatory, rigorous protocol and therefore not subject to recall bias. It is possible that the overall prevalence of neurodevelopmental disabilities may have been underreported, leading to bias to the null, but as the estimated lifetime prevalence of neurological disorders in the UK is 6% the higher prevalence (19%) found here, along with the data collection protocol, should have ensured that any effect of underreporting of ND was successfully minimised.[40] SAEs or cases of RD could also have been unreported, we feel that

this is unlikely as they would have been recorded and investigated at the time they occurred. There were a number of potentially relevant variables for which we were unable to adjust for example the incidence of RD/SAE may also be driven by provider-level characteristics such as the quality and volume of nursing care. Although it was not possible to examine the effect of individual nursing teams (e.g., their experience and training) in this analysis, we did model the contextual effect of individual wards.

Conclusions & clinical implications

Morphine-NCA is an acceptable method of postoperative analgesia in children with and without ND. Postoperative children with ND appear to be at higher risk of developing OIRD with Morphine-NCA than children without ND, although the risk remains low within the parameters of this study. Although children with ND did not experience significantly higher rates of SAE they were nevertheless 1% more likely to have a less satisfactory rating of Morphine-NCA.

(Word count 3,120)

Authors' contributions

M.A.J. designed the study, extracted the data and performed the statistical analyses. M.A.J. and R.F.H. conducted the literature search. M.A.J. and R.N. classified patients according to ND status. M.A.J., B.T., R.N. and R.F.H. contributed equally to analysis and drafting the manuscript.

Declaration of interests

None of the authors have any interests to declare.

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Figure legends

Figure 1. Posterior distributions of the effect of having neurodevelopmental disability on the risk of respiratory depression (Plot A) and serious adverse events (Plot B). CrI, credibility interval; AUC > 1, area under the curve with an odds ratio >1.

Figure 2. Plots showing the effect of morphine on the predicted probability of RD events (Plot A), and SAE (Plot B) in the NDG and CGs. Dashed lines are 95% credibility intervals (credibility intervals represent the range of plausible predicted probabilities of events across the stated range of morphine doses that are predicted by the final model). RD, respiratory depression; SAE, serious adverse events; NDG, neurodevelopmental disability group; CG, control group.

Appendix 1: Standard protocol for morphine-NCA

Morphine dose

Weight	*Dose*	*Solution*	*Dose per ml*
<50kg	1 mg kg^{-1}	50 ml of 0.9% sodium chloride or dextrose 5%	1ml = 20 mcg kg^{-1}
≥50kg	50 mg	50 ml of 0.9% sodium chloride or dextrose 5%	1ml = 1 mg

Pump programming
Background: none*, 0.2, 0.5 or 1 ml h^{-1} (0-20 mcg kg^{-1} h^{-1}, max. 1 mg h^{-1})
Bolus dose: 0.5* or 1 ml (10 or 20 mcg kg^{-1}, max. 1 mg)
Lackout: standard: 20 or 30 min. Intensive care unit only: 5 min.

* Infants and neonates <5kg.

Table 1 Patient characteristics, durations of surgery and morphine-NCA by group (NDG and CG) and NDG subgroups. NDG, neurodevelopmental disability group; OSA, obstructive sleep apnoea; CG, Control group; CP, cerebral palsy; Dev. delay, developmental delay; DS, Down's syndrome; Enceph., encephalopathy; NTD, neural tube defect; Seizure dis., seizure disorder.

Group	n	Age Median (IQR)	Weight Median (IQR)	Male n (%)	Renal impairment n (%)	OSA n (%)	Operation duration (minutes) Median (IQR)	Infusion duration (hours) Median (IQR)
CG	10 514	1.67 (0.53, 4.39)	11.00 (7.00, 16.60)	5861 (55.7%)	425 (4.0%)	20 (0.2%)	120.00 (80.00, 160.00)	27.80 (21.00, 48.30)
NDG: all	2390	6.30 (2.25, 11.16)	17.80 (11.00, 28.80)	1281 (53.6%)	89 (3.7%)	21 (0.9%)	135.00 (90.00, 190.00)	40.50 (22.20, 64.00)
CP	477	9.60 (5.27, 13.50)	21.80 (14.60, 30.00)	266 (55.8%)	1 (0.2%)	2 (0.4%)	135.00 (90.00, 190.00)	47.00 (28.00, 69.50)
Dev. delay	1399	5.60 (2.15, 10.51)	17.00 (10.62, 28.75)	759 (54.3%)	77 (5.5%)	15 (1.1%)	140.00 (90.00, 210.00)	37.90 (21.80, 64.00)
DS	163	4.00 (0.67, 9.03)	13.30 (7.20, 24.00)	90 (55.2%)	3 (1.8%)	3 (1.8%)	120.00 (90.00, 180.00)	29.00 (21.70, 47.00)
Enceph.	80	3.21 (1.13, 7.73)	12.60 (7.78, 20.00)	37 (46.3%)	1 (1.3%)	1 (1.3%)	130.00 (90.00, 180.00)	40.00 (22.63, 59.00)
NTD	160	4.53 (0.95, 8.24)	15.00 (9.15, 25.00)	79 (49.4%)	7 (4.4%)	0 (0.0%)	165.00 (108.75, 221.25)	45.00 (22.35, 65.20)
Seizure dis.	111	7.73 (2.66, 11.82)	26.00 (14.00, 37.65)	51 (45.9%)	0 (0.0%)	0 (0.0%)	180.00 (120.00, 240.00)	23.50 (19.50, 42.50)

Table 2 Postoperative morphine dose. Includes only patients without missing morphine data on day 0 (n=12 756, 99%). CG, control group; NDG, neurodevelopmental disability group.

Group	n			Median (IQR) morphine dose ($\mu g\ kg^{-1}\ hr^{-1}$)		
	D0	D1	D2	D0	D1	D2
CG	10 393	10 009	4366	15.02 (8.92, 23.48)	9.29 (4.48, 15.52)	7.19 (3.41, 13.50)
NDG: all	2363	2294	1267	16.31 (9.22, 26.04)	10.62 (5.51, 17.50)	8.12 (3.93, 14.38)
Cerebral palsy	473	465	329	19.84 (12.29, 30.37)	13.08 (8.71, 20.69)	9.15 (4.66, 15.67)
Developmental delay	1381	1333	695	15.25 (8.52, 25.00)	10.07 (5.11, 16.67)	8.00 (3.72, 14.19)
Down's syndrome	161	156	72	15.20 (8.42, 23.56)	8.92 (3.54, 16.21)	6.47 (1.42, 10.41)
Encephalopathy	78	76	44	18.01 (9.17, 26.78)	9.53 (4.75, 16.51)	5.65 (3.22, 13.00)
Neural tube defects	160	155	96	18.51 (9.46, 26.92)	11.30 (5.12, 19.78)	8.70 (4.70, 15.51)
Seizure disorder	110	109	31	12.56 (8.43, 21.45)	8.86 (4.85, 12.97)	6.30 (2.02, 10.21)

Table 3 Respiratory depression and serious adverse events by group and sub-group. NDG, neurodevelopmental disability group; CG, control group.

		NDG	CG (n=10 514)
Respiratory depression	NDG: all (n=2390)	26 (1.09%)	62 (0.59%)
	Cerebral palsy (n=477)	8 (1.68%)	
	Developmental delay (n=1399)	11 (0.79%)	
	Down's syndrome (n=163)	3 (1.84%)	
	Encephalopathy (n=80)	2 (2.53%)	
	Neural tube defects (n=160)	2 (1.25%)	
	Seizure disorder (n=111)	0 (0.00%)	
Serious adverse events	NDG: all (n=2390)	14 (0.59%)	38 (0.36%)
	Cerebral palsy (n=477)	6 (1.26%)	
	Developmental delay (n=1399)	4 (0.29%)	
	Down's syndrome (n=163)	2 (1.23%)	
	Encephalopathy (n=80)	1 (1.25%)	
	Neural tube defects (n=160)	1 (0.63%)	
	Seizure disorder (n=111)	0 (0.00%)	

On-line Tables

On-line Table 1. Diagnoses of patients with ND (n=2390) where at least 80 patients with the same diagnosis were recorded. Groups where no cause was specified or where fewer than 80 patients had a particular diagnosis are grouped as developmental delay.

Diagnosis	n
Cerebral palsy	477
Developmental delay	1399
Down's syndrome	163
Encephalopathy	80
Neural tube defect	160
Seizure disorder	111

On-line Table 2. Number of patients undergoing each type of surgery broken down by diagnostic category (row percentages). CG, control group; NDG, neurodevelopmental disability group.

Group	n	Cardiothoracic n (%)	General Surgery n (%)	Urology n (%)	Head & Neck n (%)	Neurosurgery n (%)	Orthopaedics n (%)	Plastics n (%)
CG	10 514	1361 (12.9%)	3348 (31.8%)	2185 (20.8%)	1331 (12.7%)	663 (6.3%)	1495 (14.2%)	131 (1.3%)
NDG: all	2390	137 (5.7%)	933 (39.0%)	173 (7.2%)	143 (6.0%)	287 (12.0%)	707 (29.6%)	10 (0.4%)
Cerebral palsy	477	3 (0.6%)	200 (41.9%)	9 (1.9%)	2 (0.4%)	6 (1.2%)	257 (53.9%)	0 (0.0%)
Developmental delay	1399	93 (6.6%)	549 (39.2%)	119 (8.5%)	122 (8.7%)	143 (10.2%)	367 (26.2%)	6 (0.4%)
Down's syndrome	163	34 (20.9%)	90 (55.2%)	5 (3.1%)	5 (3.1%)	9 (5.5%)	20 (12.3%)	0 (0.0%)
Encephalopathy	80	2 (2.5%)	50 (62.5%)	0 (0.0%)	11 (13.8%)	6 (7.5%)	11 (13.8%)	0 (0.0%)
Neural tube defects	160	1 (0.6%)	19 (11.9%)	37 (23.1%)	0 (0.0%)	60 (37.5%)	39 (24.4%)	4 (2.5%)
Seizure disorder	111	4 (3.6%)	25 (22.5%)	3 (2.7%)	3 (2.7%)	63 (56.8%)	13 (11.7%)	0 (0.0%)

On-line Table 3. Intraoperative opioid administration and dosing. Includes only patients with intraoperative opioid data (n=11,946, 93%). The 'other' category represents a small number of patients who were given diamorphine or codeine. NDG, neurodevelopmental disability group; CG control group. * Dose-by-group data were also stratified by age (≤12 years and >12 years) and the results were the same (not shown).

Drug	NDG n (%) or median (IQR)	CG n (%) or median (IQR)
Drug administered		
Any opioid	2001 (89.3%)	8522 (87.8%)
Morphine	921 (41.1%)	3434 (35.4%)
Fentanyl	1631 (72.8%)	7121 (73.4%)
Other	4 (0.2%)	22 (0.2%)
Dose ($mg \cdot kg^{-1}$)*		
Morphine	0.10 (0.07, 0.12)	0.10 (0.06, 0.11)
Fentanyl	0.003 (0.002, 0.004)	0.003 (0.002, 0.005)

On-line Table 4. Morphine dose by surgery in patients in the neurodevelopmental disability group. Includes only patients without missing morphine data on day 0 (n=2,363, 99%).

Surgical category	n			Median (IQR) morphine dose ($\mu g\ kg^{-1}\ hr^{-1}$)		
	D0	D1	D2	D0	D1	D2
Cardiothoracic	132	126	52	18.87 (11.92, 29.09)	14.33 (8.92, 21.46)	11.13 (6.54, 18.02)
General	927	916	613	16.73 (9.95, 26.50)	10.19 (5.33, 16.93)	6.60 (3.14, 11.67)
Urological	172	161	96	15.64 (7.74, 24.91)	10.00 (5.00, 17.00)	8.29 (3.73, 15.58)
Head and neck	141	134	10	8.31 (4.98, 12.86)	3.03 (1.25, 6.08)	1.49 (0.00, 4.22)
Neurosurgery	285	277	83	12.32 (6.67, 21.29)	8.27 (4.63, 13.08)	6.00 (3.28, 10.11)
Orthopaedic	696	671	411	18.84 (11.96, 28.64)	13.36 (8.50, 21.00)	10.67 (6.15, 17.87)
Plastics	10	9	2	8.98 (4.38, 22.29)	6.31 (5.83, 12.08)	5.13 (4.84, 5.42)

On-line Table 5. Morphine dose by surgery in patients in the control group. Includes only patients without missing morphine data on day 0 (n=10,393, 99%).

Surgical category	n			Median (IQR) morphine dose ($\mu g\ kg^{-1}\ hr^{-1}$)		
	D0	D1	D2	D0	D1	D2
Cardiothoracic	1332	1281	614	20.25 (12.36, 30.00)	15.25 (10.00, 20.83)	11.09 (6.51, 16.62)
General	3306	3204	2045	15.00 (8.21, 23.63)	9.09 (4.25, 15.30)	5.75 (2.31, 11.08)
Urological	2,173	2,103	670	13.64 (8.45, 20.53)	8.02 (4.00, 12.71)	5.87 (3.29, 12.16)
Head and neck	1,319	1,230	71	10.61 (6.80, 15.80)	4.44 (2.00, 8.01)	3.27 (0.85, 8.18)
Neurosurgery	651	637	299	19.05 (11.47, 27.06)	11.47 (6.78, 16.92)	7.41 (3.90, 12.58)
Orthopaedic	1483	1437	632	17.33 (11.11, 26.58)	11.43 (7.23, 18.42)	10.90 (5.20, 20.93)
Plastics	129	117	35	13.13 (7.65, 19.56)	8.33 (3.90, 13.47)	7.54 (4.14, 11.91)

On-line Table 6. Initial background and bolus doses. Includes patients with background and bolus dose data only. NDG, neurodevelopmental disability group; CG control group. * The distribution of bolus sizes was bimodal with most patients having either a 10 $\mu g \cdot kg^{-1}$ or 20 $\mu g \cdot kg^{-1}$ bolus. A higher proportion of patients in the CG had a bolus size of 10 $\mu g \cdot kg^{-1}$ (25%) than patients in the NDG (15%), this difference being reflected in the lower end of the IQRs. Note also that the distribution of initial background rate was trimodal at the standard settings of 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$, 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$. These data were treated as continuous as any value along a range was theoretically possible and there were a number of patients whose bolus sizes and backgrounds were out of the usual protocol.

Program	NDG n (%) or median (IQR)	CG n (%) or median (IQR)
Commenced on background infusion	1648 (69.0%)	7075 (67.6%)
Initial background rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$)*	10.0 (4.0, 10.0)	10.0 (4.0, 10.0)
Initial bolus size ($\mu g \cdot kg^{-1}$)*	20.0 (20.0, 20.0)	20.0 (10.0, 20.0)

On-line Table 7. Day of occurrence of respiratory depression and serious adverse events. NDG neurodevelopmental disability group; CG control group.

Respiratory depression

Day	NDG n (%)	CG n (%)
0	13 (50%)	29 (47%)
1	12 (46%)	27 (44%)
2	1 (4%)	5 (8%)
3	0 (0%)	0 (0%)
4	0 (0%)	1 (2%)

Serious adverse events

Day	NDG n (%)	CG n (%)
0	9 (64%)	18 (47%)
1	5 (36%)	16 (42%)
2	0 (0%)	4 (11%)

On-line Table 8. Distribution of respiratory depression and serious adverse events in the neurodevelopmental disability group and control group, per predictors. Denominator = number of patients at each predictor level within the neurodevelopmental disability group or control group. NDG, neurodevelopmental disability group; CG, control group.

		Respiratory depression		Serious adverse events	
	Predictor	NDG n (%)	CG n (%)	NDG n (%)	CG n (%)
Age category	<1 mo	2/38 (5.3%)	21/583 (3.6%)	1/38 (2.6%)	16/583 (2.7%)
	1-36 mo	4/690 (0.6%)	26/6118 (0.4%)	2/690 (0.3%)	12/6118 (0.2%)
	3-6 yr	6/574 (1.0%)	7/2535 (0.3%)	2/574 (0.3%)	5/2535 (0.2%)
	7-10 yr	4/473 (0.8%)	2/735 (0.3%)	3/473 (0.6%)	1/735 (0.1%)
	11-15 yr	8/497 (1.6%)	4/472 (0.8%)	5/497 (1.0%)	3/472 (0.6%)
	≥16yr	2/118 (1.7%)	2/71 (2.8%)	1/118 (0.8%)	1/71 (1.4%)
Sex	Male	15/1282 (1.2%)	38/5861 (0.6%)	8/1282 (0.6%)	23/5861 (0.4%)
	Female	11/1108 (1.0%)	24/4653 (0.5%)	6/1108 (0.5%)	15/4653 (0.3%)
Surgery	Cardiothoracic	1/137 (0.7%)	4/1363 (0.3%)	1/137 (0.7%)	3/1363 (0.2%)
	General	13/933 (1.4%)	38/3348 (1.1%)	7/933 (0.8%)	20/3348 (0.6%)
	Urological	0/173 (0.0%)	6/2185 (0.3%)	0/173 (0.0%)	5/2185 (0.2%)
	Head and neck	0/143 (0.0%)	5/1331 (0.4%)	0/143 (0.0%)	4/1331 (0.3%)
	Neurosurgery	1/287 (0.3%)	5/663 (0.8%)	0/287 (0.0%)	5/663 (0.8%)
	Orthopaedic	11/707 (1.6%)	4/1495 (0.3%)	6/707 (0.8%)	1/1495 (0.1%)
	Plastics	0/10 (0.0%)	0/131 (0.0%)	0/10 (0.0%)	0/131 (0.0%)
Renal failure	Yes	0/89 (0.0%)	3/425 (0.7%)	0/89 (0.0%)	2/425 (0.5%)
	No	26/2301 (1.1%)	59/10089 (0.6%)	14/2301 (0.6%)	36/10089 (0.4%)
Obstructive sleep apnoea	Yes	0/21 (0.0%)	1/20 (0.1%)	0/21 (0.0%)	0/20 (0.0%)
	No	26/2369 (0.0%)	61/10494 (0.0%)	14/2369 (0.0%)	38/10494 (0.0%)
Intraoperative opioid	Yes	20/2001 (1.0%)	51/8521 (0.6%)	11/2001 (0.5%)	33/8521 (0.4%)
	No	3/239 (0.8%)	4/1183 (0.3%)	1/240 (0.4%)	2/1183 (0.2%)
Background infusion	Yes	21/1648 (1.3%)	32/7075 (0.5%)	11/1648 (0.7%)	18/7075 (0.3%)
	No	5/739 (0.7%)	30/3398 (0.9%)	3/739 (0.4%)	20/3398 (0.6%)

On-line Table 9. Associations between postoperative morphine dose ($\mu g \cdot kg^{-1} \cdot hr^{-1}$) and respiratory depression and serious adverse events. RD, respiratory depression; SAE, serious adverse events; NDG, neurodevelopmental disability group; CG, control group.

	Respiratory depression		Serious adverse events	
Group	RD Median (IQR)	No RD Median (IQR)	SAE Median (IQR)	No SAE Median (IQR)
NDG	27.54 (11.41, 36.20)	16.20 (9.23, 25.81)	27.77 (3.42, 39.49)	16.30 (9.23, 25.96)
CG	10.00 (5.63, 17.39)	15.05 (8.94, 23.53)	10.00 (5.00, 16.20)	15.04 (8.94, 23.53)

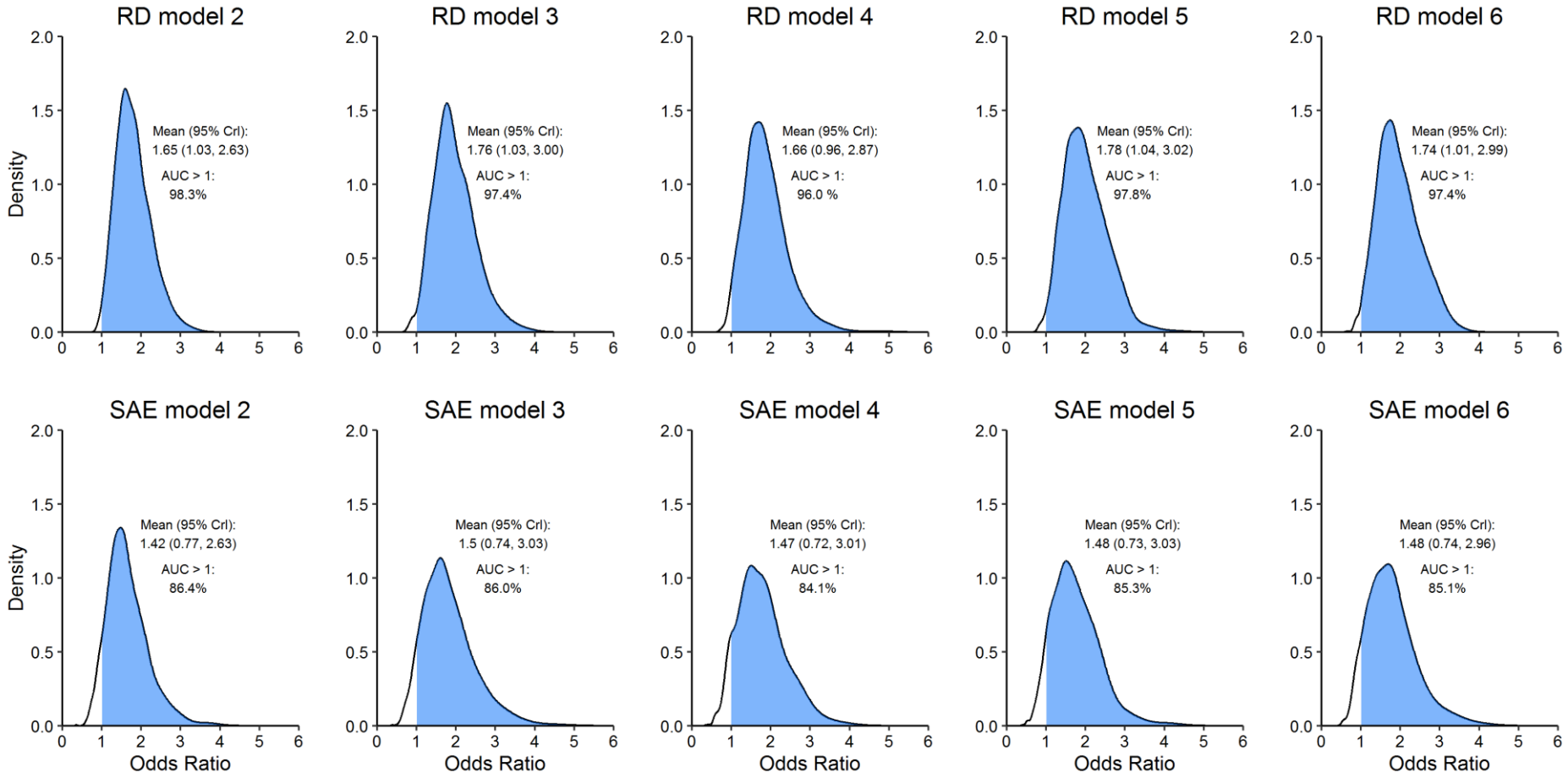
On-line Table 10 Logistic regression models of respiratory depression. Shaded coefficients are those whose 95% credible intervals (1.96 x SD) do not contain 0. All posteriors were approximately Gaussian other than ward intercept SD which was slightly right-skewed. RD, respiratory depression; ND,

Outcome (n, %)	N	Predictor		1	2	3	4	5	6	7
				Mean (SD) logistic coefficient estimates from posterior distributions						
RD	Patients	Intercept		-5.31 (0.26)	-5.40 (0.27)	-3.71 (0.34)	-4.20 (0.56)	-3.79 (0.53)	-3.67 (0.39)	-3.42 (0.32)
(88, 0.69%)	12 904	Neurological deficit (yes *vs* no)			0.50 (0.24)	0.57 (0.27)	0.51 (0.28)	0.58 (0.27)	0.55 (0.28)	-0.30 (0.44)
		Age	<1 mo			Reference	Reference	Reference	Reference	Reference
	Wards		1-36 mo			-2.04 (0.30)	-1.91 (0.30)	-2.09 (0.34)	-2.03 (0.30)	-1.95 (0.33)
	38		3-6 yr			-2.15 (0.39)	-1.99 (0.40)	-2.21 (0.44)	-2.14 (0.39)	-2.04 (0.41)
			7-10 yr			-2.19 (0.52)	-2.02 (0.51)	-2.22 (0.55)	-2.15 (0.52)	-2.05 (0.54)
			11-15 yr			-1.30 (0.43)	-1.10 (0.44)	-1.35 (0.47)	-1.29 (0.44)	-1.22 (0.46)
			16+ yr			-0.88 (0.61)	-0.74 (0.61)	-0.99 (0.66)	-0.89 (0.61)	-0.88 (0.66)
		Gender (Male *vs* female)				0.16 (0.23)				
		Renal failure (yes *vs* no)				-0.32 (0.66)				
		Obstructive sleep apnoea (yes *vs* no)				0.77 (1.28)				
		Surgery	Cardiothoracic				Reference			
			General				0.93 (0.56)			
			Urological				-0.18 (0.68)			
			Head, neck & plastics				0.10 (0.71)			
			Neurosurgery				0.30 (0.70)			
			Orthopaedic				0.49 (0.62)			
		Intraoperative opioid (yes *vs* no)						0.35 (0.39)		
		Background infusion (yes *vs* no)						0.20 (0.29)		
		Bolus size (per mL)						-0.01 (0.03)		
		Morphine dose D0 (μg kg^{-1} hr^{-1})						0.00 (0.01)		-0.02 (0.01)
		Year							0.01 (0.03)	
		Morphine dose x ND interaction								0.04 (0.02)
	Random	Ward intercept SD		0.78 (0.26)	0.77 (0.27)	0.48 (0.22)	0.30 (0.22)	0.45 (0.23)	0.45 (0.21)	0.44 (0.22)
		DIC		1032.7	1031.2	1001.7	1000.7	1004.8	1000.5	995.2

neurodevelopmental disability; DIC, deviance information criterion.

Outcome (n, %)	N	Effects	Predictor	1	2	3	4	5	6	7
				Mean (SD) logit coefficient estimates from posterior distributions						
SAE	Patients	Fixed	Intercept	-5.81 (0.29)	-5.86 (0.28)	-3.97 (0.38)	-4.23 (0.69)	-4.37 (0.74)	-3.94 (0.46)	-3.58 (0.36)
(52, 0.40%)	12 904		Neurological deficit (yes *vs* no)		0.35 (0.31)	0.40 (0.36)	0.39 (0.37)	0.39 (0.37)	0.39 (0.36)	-0.78 (0.59)
			Age <1 mo			Reference	Reference	Reference	Reference	Reference
	Wards		1-36 mo			-2.53 (0.40)	-2.47 (0.40)	-2.50 (0.44)	-2.52 (0.39)	-2.29 (0.41)
	38		3-6 yr			-2.46 (0.48)	-2.42 (0.52)	-2.44 (0.56)	-2.48 (0.50)	-2.21 (0.51)
			7-10 yr			-2.29 (0.61)	-2.12 (0.64)	-2.20 (0.68)	-2.78 (0.60)	-1.95 (0.66)
			11-15 yr			-1.31 (0.50)	-1.16 (0.55)	-1.25 (0.58)	-1.32 (0.51)	-1.05 (0.57)
			16+ yr			-1.32 (0.91)	-1.16 (0.93)	-1.25 (0.93)	-1.27 (0.87)	-1.10 (0.92)
			Gender (Male *vs* female)			0.12 (0.29)				
			Renal failure (yes *vs* no)			-0.30 (0.89)				
			Surgery Cardiothoracic				Reference			
			General				0.32 (0.63)			
			Urological				0.09 (0.81)			
			Head, neck & plastics				0.35 (0.84)			
			Neurosurgery				0.53 (0.82)			
			Orthopaedic				-0.13 (0.76)			
			Intraoperative opioid (yes *vs* no)					0.82 (0.60)		
			Background infusion (yes *vs* no)					0.21 (0.36)		
			Bolus size (per mL)					-0.02 (0.03)		
			Morphine dose D0 (μg kg^{-1} hr^{-1})					-0.01 (0.01)		-0.04 (0.02)
			Year						0.01 (0.03)	
			Morphine x ND interaction							0.06 (0.02)
		Random	Ward intercept SD	0.71 (0.29)	0.69 (0.26)	0.44 (0.26)	0.50 (0.29)	0.42 (0.24)	0.43 (0.26)	0.44 (0.24)
			DIC	669.1	669.0	640.1	643.9	641.1	638.1	632.6

On-line Table 11 Logistic regression models of serious adverse events. Shaded coefficients are those whose 95% credible intervals (1.96 x SD) do not contain 0. All posteriors were approximately Gaussian other than ward intercept SD which was slightly right-skewed. SAE, serious adverse events; ND, neurodevelopmental disability; DIC, deviance information criterion.



On-line Figure 1. Posterior distributions of the effect of having neurodevelopmental disability on the risk of respiratory depression (first row) and serious adverse events (second row). See On-Line Tables 10 and 11 for details of the models. AUC > 1, area under the curve with an odds ratio >1.

On-line Statistical Appendix

This Appendix gives the full details of the statistical methodology used in the analysis. Superscript numbers refer to references at the end of this document and not in the main manuscript. All analyses were conducted in R (Vienna, Austria: R Foundation for Statistical Computing, 2016) and WinBUGS (Cambridge, UK: Medical Research Council Biostatistics Unit, 2003). WinBUGS was interfaced with R using the *R2WinBUGS* package[1] and trace plots generated using *mcmcplots*.[2] All other graphics were created using *ggplot2*.[3] Data were obtained and analysed on all available patients.

Descriptive statistics

Descriptive statistics were computed as median (IQR) and n (%). Possible effect modifiers were investigated using stratification (On-line Tables 8 and 9). Substantial differences in the stratified data were treated as evidence of effect modification and such variables treated as candidates for interaction in the regression modelling. Day 0 postoperative morphine dose was taken forward in such a way.

Missing data

There were missing data on the following variables: operation duration (n=1037, 8.0%), intraoperative opioid administration (n=958, 7.4%), infusion background, background rate and bolus size (n=44, 0.3% on all three) and overall day 0 postoperative morphine dose (n=148, 1.1%). The mechanism was considered to be either missing completely at random (MCAR; for example, some data were not entered because a chart was missing or illegible and these appeared to be isolated incidents) or missing at random (MAR). Missingness for operation duration and intraoperative opioid administration, for example, was associated with surgical category and no mechanism relating to the missing values was postulated.

Given that the MAR/MCAR assumption appeared reasonable, and in order to mitigate the loss of power and bias inherent in complete case analysis, expectation-maximisation multiple imputation with bootstrapping using the R package *Amelia II*[4] was performed to impute missing values with ten imputed datasets. The imputation model was given flat priors (the default in *Amelia II*) though logical bounds were set as appropriate to ensure impossible values were not imputed. Lognormal variables were transformed during the imputation process and histograms of the observed data overlaid with density curves of the imputed data indicated that the imputations were reasonable. Where models were constructed from imputed datasets, parameter and variance estimates were combined using Rubin's rules.

Regression modelling: Bayesian set-up

Multilevel logistic regression was used to analyse the incidence of RD and SAEs. Because of the complexity of these models, we used Markov chain Monte Carlo simulations with Gibbs sampling to carry out Bayesian inference of model parameters. All estimands, other than level-two variance, were given non-informative normally distributed priors (mean 0, precision[*] 0.01 or 0.001—a smaller precision was required for some parameters as the larger sometimes failed). Level-two variance was ~ $N(0, \sigma_\alpha)$ where the hyperparameter σ_α was ~ U(0, 10) to coerce it to a positive value.[5] Our use of non-informative priors was motivated by a lack of available information on which to reliably base informative ones.

Three chains were simulated with randomly generated overdispersed starting values and with a sufficient number of burn-in and substantive iterations until convergence. For the most complex models, 4000 burn-in and 22 000 further iterations were adequate. Convergence was

[*] Precision is the inverse of the variance and therefore a precision of 0.001 = a variance of 1/0.001 = 1,000. Precision is simply the way in which the normal distribution is parameterised in BUGS.

assessed by visually examining trace plots and by ensuring that, for all parameters, the Gelman-Rubin $\hat{R}$ statistic was <1.1.

Regression modelling: model specification

Models were constructed in the following order: first, a null intercept-only model. Whether the patient had ND was then entered and retained in all subsequent models. Variables were then added in conceptually appropriate groups: age, gender, renal failure and obstructive sleep apnoea; surgical category; intraoperative and postoperative morphine administration/doses; and, in order to account for unmeasured changes in practice over time, year. Predictors were discarded if their 95% credible intervals contained 0. Where there was evidence of effect modification, this was tested after constructing the main effects models by entering an interaction term.

In all models, the intercept was allowed to vary by ward. This was necessary to account for the structured nature of the data (patients nested in wards). This also enables the examination of inter-ward variation and accounts for unmeasured provider-level factors which may influence the risk of RD/SAE.

Model fit was assessed by examining the deviance information criterion (DIC) of each model. The DIC is a goodness of fit measure which accounts for model complexity: lower values represent better fit; a change in five units indicates some substantial improvement and a change in ten units indicates definite improvement.

Operation duration was omitted from the models as it was felt that including it would have been an over-adjustment beyond type of surgery and intraoperative opioid administration. We

did not include dose of intraoperative opioid because although patients in the NDG were more likely to receive intraoperative morphine (On-line Table 3), there were no differences between the two groups in doses; we therefore only included a binary variable indicating whether or not each patient received opioids during surgery. A binary variable indicating whether the patient was started with a background infusion, and not the background rate, was included for the same reason. Finally, OSA was not entered into the SAE model because there were no patients with OSA who experienced an SAE (On-line Table 7).

The posterior distributions for parameter estimates are presented with their mean and SD. The mean gives the most likely value of each parameter, which in turns represents the change in the log-odds of RD with each unit increase in the predictor; analogously to classical logistic regression, the exponent of the null model intercept gives the baseline odds and coefficients can be exponentiated to obtain odds ratios (though presence of interaction terms complicates interpretation). In every model, the ward intercept SD is a measure of the extent to which the risk of RD varies by ward (after taking into account the variables in the model). Figure 2 of the manuscript was generated by taking 1000 simulated draws from the posterior distributions of the logit estimates. The dashed lines represent 95% credibility limits obtained from the 2.5^{th} and 97.5^{th} percentiles of the posterior draws.

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