Check for updates

Original Article

Characteristics of children aged 2–17 years undergoing anaesthesia in Danish hospitals 2005–2015: a national observational study

C. Strøm,[1,2] **L. H. Lundstrøm,**[3] **A. Afshari**[4] and **N. Lohse**[2]

1 Resident, Department of Anaesthesia, Holbaek Hospital, University of Copenhagen, Denmark
2 Resident, Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet, University of Copenhagen, Denmark
3 Senior Consultant, Department of Anaesthesiology, Hilleroed Hospital, University of Copenhagen, Denmark
4 Senior Consultant, Department of Anaesthesiology, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Denmark

Summary

Provision of paediatric anaesthesia requires careful consideration of the child's cognitive state, unique body composition and physiology. In an observational cohort study, we describe the population characteristics and conduct of anaesthesia in children aged 2–17 years from 1 January 2005 to 31 December 2015. Children were identified from the Danish Anaesthesia Database. We recorded the following variables: age; sex; comorbidities; indications for anaesthesia; practice of anaesthesia; and complications. Results are presented for two age groups: 2–5 and 6–17 years. In total, 32,840 (61% male) children aged 2–5 years received 50,484 anaesthesia episodes and 91,418 (54% male) children aged 6–17 years received 141,082 anaesthesia episodes. The younger children, compared with the older children, were more frequently anaesthetised at a university hospital (50% vs. 36%) and for non-surgical procedures (24% vs. 8%). For both age groups, general anaesthesia was the primary choice of anaesthesia regardless of the reason for anaesthesia. For surgery, general anaesthesia using inhalational agents in addition to intravenous agents or alone was more frequently used in younger children (49% vs. 15%), whereas older children commonly received total intravenous anaesthesia (50% vs. 83%). Regional anaesthesia was infrequently utilised. Complications occurred in 3.3% of anaesthesia episodes among 2–5 year olds compared with 3.7% of anaesthesia episodes among children aged 6–17 years. In conclusion, we found younger children (aged 2–5), compared with older children (aged 6–17) were more frequently anaesthetised for non-surgical reasons, at a university hospital and using inhalational agents. Complications were rare.

Correspondence to: C. Strøm
Email: camilla007@gmail.com
Accepted: 4 July 2018
Keywords: paediatrics: airway management; paediatrics: postoperative regional analgesia; practice standards: definition
Twitter: @dr_stroem

Introduction

Millions of children receive anaesthesia each year for surgery and other medical procedures in order to facilitate necessary and urgent treatments which would otherwise be either impossible to conduct or might be a traumatic experience for the child and their family. Provision of anaesthesia requires careful consideration of the child's cognitive state, body composition and physiology [1].

© 2018 Association of Anaesthetists

Minor procedures and examinations, such as insertion of peripheral intravenous (i.v.) lines, joint injections or MRI scans, may require anaesthesia or deep sedation in order to obtain optimal results and patient comfort. Quality of care in paediatric anaesthesia practice has gained increasing attention in recent years. Large multinational population-based studies have investigated short- and long-term complications of paediatric anaesthesia [2–4], and initiatives such as the Safe-tots project for smaller children (aged under 3 years) have been established to disseminate principles of safe conduct of paediatric anaesthesia [5]. Meanwhile, the published literature still fails to address the recent associations between population characteristics and actual conduct of anaesthesia, for example, the choice of anaesthetic approach for various procedures and implications of anaesthetic care in children. The aim of this study was to describe the population of children receiving anaesthesia in Denmark, recent paediatric anaesthetic practice, for example, the choice of anaesthesia and airway management, and to report the incidence and types of anaesthesia-associated complications for children aged 2–17 years. In a previous publication, we reported data for the youngest children (age < 2 years) [6]. The choice of age cut-off represents the national criteria as defined by the Danish Health Authority [7].

Methods

We conducted a population-based cohort study in which we describe the anaesthetic management of children aged 2–17 years over a period of 11 years from 2005 to 2015 in Denmark. We divided the population into two sub-groups, 2–5 and 6–17 years old due to marked anatomical andphysiological developmental changes within each paediatric age range. This study is reported according to the Strengthening EACH Reporting of Observational Studies in Epidemiology (STROBE) guidelines [8].

Healthcare is primarily provided through a single-payer healthcare system at public hospitals in Denmark. We combined information from three nationwide databases, the Danish Anaesthesia Database (DAD) [9], the Danish Civil Registration System (DCRS) [10] and the Danish National Patient Registry (DNPR) [11]. The Steering Committee of DAD and the Danish Data Protection Agency approved the study. According to Danish law for registry-based research, Research Ethics Committee approval and individual written informed consent was not required.

The DAD is a clinical quality assurance database which contains information on patients undergoing sedation and anaesthesia under the care of certified anaesthesia personnel [9]. The DAD covers approximately 80% of all anaesthetic episodes in Denmark [9]. The DAD captures data from pre-operative assessment until the end of the patient's stay in the recovery area [9]. This includes type of anaesthesia, choice of airway management and complications. The DAD was updated on 1 April 2008, when details on facemask ventilation, Cormack–Lehane scores [12] for difficult tracheal intubations and complications, defined as cardiac arrest, death during anaesthesia, dental injury, eye injury, itching, urinary retention and seizures, were added. The following complications were removed from the database at the same time: pain with visual assessment score above 5; and postoperative nausea and vomiting. A stepwise update was launched during 2015. We retrieved data from the previous version of the DAD database, which included two of the five Danish regions (Region Zealand and Central Denmark Region) in the period from 1 February 2015 to 31 December 2015. The DCRS contains continuously updated information on name, date of birth, addresses and date of death of all Danish residents [10]. Danish citizens are assigned a unique personal identification number at birth (CPR number) [13] that is used in all contacts with public administration and constitutes a link between all Danish registries. The DNPR is a registry documenting all hospitalisations in Denmark [11], including time of hospital admission and discharge, diagnoses (using The World Health Organization International Classification of Diseases version 10) [14] and codes for surgical procedures using the Danish version of the Nordic Classification for Surgical Procedures [15].

We defined an anaesthetic case to be any episode of anaesthesia in Denmark identified through the DAD. We retrieved consecutive patients aged 2–17 years between 1 January 2005 and 31 December 2015. Data from DAD were linked with data from the DCRS and the DNPR via the patient's CPR number. We recorded the number of anaesthesia episodes in total and for each child. For each anaesthesia episode we recorded the following baseline characteristics: age; height; weight; sex; ASA physical status [16]; Charlson comorbidity index (CCI) [17]; and the total number of days spent in hospital within the 6 months before anaesthesia (ranging from 0 to 180 days). We added the total number of days spent in hospital during the previous 6 months as an additional measure of comorbidity, because ASA physical status and CCI are indices developed for adult patients and their application in paediatric practice is unclear. We also recorded the academic status of the hospital (non-university/university/public/private), the indication for anaesthesia and type of anaesthesia (general/regional/sedation/combined general and regional/combined regional and sedation.

 © 2018 Association of Anaesthetists

In general anaesthetic cases, we recorded the type of anaesthetic (inhalational/i.v./i.v. in combination with other inhalational agent/i.v. in combination with nitrous oxide/ rectal or intramuscular). In cases of regional anaesthesia we registered the method, for example, spinal, epidural and interscalene brachial plexus nerve block. For cases of general anaesthesia (alone or in combination with regional anaesthesia), we recorded the type of airway management (spontaneous breathing/facemask ventilation/supraglottic airway device (SAD)/tracheal intubation/tracheostomy). The use and choice of neuromuscular blocking drugs was also obtained. For tracheal intubations, the number of intubation attempts and intubation device (Macintosh laryngoscope/videolaryngoscope/other device) was recorded. Cormack and Lehane scores were obtained in difficult airway management situations. We recorded the use and ease of facemask ventilation (no attempt/easy/difficult/not defined). The use of regional anaesthesia and supraglottic airway devices over the study period (number of cases per year) was plotted.

Complications occurring in the operating theatre and in the recovery area were recorded and included: airway (aspiration, cannot intubate cannot oxygenate (CICO), dental injury, difficult tracheal intubation and prolonged neuromuscular blockade); respiratory; circulatory (cardiac arrest, central venous catheter misplacement, death during anaesthesia, pneumothorax, pulmonary oedema and respiratory insufficiency, new onset); central nervous system; peripheral nervous system (accidental dural puncture, insufficient regional anaesthesia (insufficient to ensure peri-operative or postoperative pain control), nerve damage due to patient positioning (peripheral nerve injuries suspected to be caused by inappropriate positioning during surgery), pain (visual assessment score above five) and awareness); allergic reactions including anaphylaxis and itching; and other (disruption of anaesthesia (if anaesthesia was interrupted in order to awaken the patient), hypothermia (core body temperature below 36 °C), malignant hyperthermia, medication error (administration of wrong drug or dose), urinary retention, postoperative nausea and vomiting and other complications not defined elsewhere). We defined serious adverse events to be the occurrence of any of the following: cardiac arrest, CICO situation or death.

In Denmark, two qualified personnel are required at induction and emergence of general anaesthesia in children. These are usually a certified nurse anaesthetist and either a certified anaesthesia specialist or a doctor training in anaesthesia. We recorded the level of seniority and training of the anaesthetists responsible for the anaesthesia.

Results

A total of 32,840 children aged 2–5 years (61.20% of whom were male, 95%CI 60.67–61.73%) received 50,484 anaesthetic episodes, and 91,418 children aged 6–17 years (53.91% of whom were male, 95%CI 53.58–54.22%) received 141,082 anaesthetic episodes between 1 January 2005 and 31 December 2015 in Danish hospitals that report to the DAD. Overall, 20,925 anaesthesia cases (41.45%, 95%CI 41.02–41.88%) in children aged 2–5 years and 49,664 anaesthesia cases (35.20%, 95%CI 34.95–35.45) in children aged 6–17 years were performed in children with previous anaesthesia exposure. Characteristics of the children are shown in Table 1.

The number of cases performed in children aged 2–5 years compared with children aged 6–17 years at non-university public hospitals 25,253 (50.02%, 95%CI 49.58–50.46) vs. 87,525 (62.04%, 95%CI 61.79–62.29); university public hospitals 25,030 (49.58%, 95%CI 49. 14–50.02) vs. 50,891 (36.1%, 95%CI 35.82–36.32); private hospitals 165 (0.33%, 95%CI 0.28–0.38) vs. 2180 (1.55%, 95%CI 1.49–1.62); and no information on hospital status occurred in 36 (0.07%, 95%CI 0.05–0.10) vs. 486 (0.34%, 95%CI 0.31–0.37). Non-surgical procedures were more common in children aged 2–5 years compared with children aged 6–17 years; 2–5 years: n = 11,917 (23.61%, 95%CI 23.24–23.98) vs. 6–17 years: 11,456 (8.12%, 95%CI 7.98–8.26). Overview of the type of anaesthesia and the corresponding procedures is presented in Fig. 1 for children aged 2–5 years and in Fig. 2 for children aged 6–17 years. The choice of anaesthesia agents used for general anaesthesia is presented in Fig. 3 for children aged 2–5 years and in Fig. 4 for children aged 6–17 years. Total i.v. anaesthesia was more frequently used in older children compared with younger children, regardless of the reason for anaesthesia.

Airway management was registered in cases of general anaesthesia (alone or in combination with regional anaesthesia). For both age groups, use of a supraglottic airway device was the most frequent airway management method, followed by tracheal intubation. Facemask ventilation at any stage of airway management was registered in 37,951 cases (78.30%, 95%CI 77.93–78.66) for children aged 2–5 years and in 111,012 cases (80.80%; 95%CI 80.59–81.01) for those aged 6–17 years. Difficult facemask ventilation was recorded in 20 cases (0.04%, 95%CI 0.03–0.06) in children aged 2–5 years compared with 24 cases (0.10%, 95%CI 0.01–0.03) in children aged 6–17 years (Table 2). The use of supraglottic airway devices over time is presented in Fig. 5.

© 2018 Association of Anaesthetists

Table 1 Characteristics of children aged 2–5 years and 6–17 years anaesthetised in Denmark between 2005 and 2015 and the 10 most common indications for anaesthesia. A total of 32,840 children aged 2–5 years received 50,484 anaesthetic episodes and 91,418 children aged 6–17 years received 141,082 anaesthetic episodes. Values are median (IQR [range]) or number (proportion).

Variable		2–5 years old			6–17 years old	
			95%CI			95%CI
Age; years		4 (3–5 [2–5])	N/A		12 (9–15 [6–17])	N/A
Missing		0			0	
Height; cm		105 (98–116 [78–132])	N/A		158 (137–170 [94–198])	N/A
Missing		157 [0.31%]	0.27–0.36		302 [0.21%]	0.19–0.24
Weight; kg		16.5 (14.0–19.5 [9.0–30.9])	N/A		45 (30–60 [13–100])	N/A
Missing		141 [0.28%]	0.24–0.33		309 [0.22%]	0.20–0.25
Charlson comorbidity index						
0		38,392 [76.05%]	75.68–76.43		112,918 [80.04%]	79.83–80.25
1		4775 [9.46%]	9.21–9.72		15,629 [11.08%]	10.92–11.24
2		5307 [10.51%]	10.25–10.78		7672 [5.44%]	5.32–5.56
3+		1569 [3.11%]	2.96–3.27		3736 [2.65%]	2.57–2.74
Missing		441 [0.87%]	0.79–0.95		1127 [0.80%]	0.75–0.85
Days in hospital prior to anaesthetic episode						
0 days		10,612 [21.02%]	20.67–21.38		33,133 [23.48%]	23.26–23.70
1 day		19,815 [39.25%]	38.82–39.68		66,283 [46.98%]	46.72–47.24
2 days		5491 [10.88%]	10.61–11.15		14,763 [10.46%]	10.30–10.62
3 to 9 days		7908 [15.66%]	15.35–15.98		16,975 [12.03%]	11.86–12.20
10 to 24 days		3047 [6.04%]	5.84–6.25		5116 [3.63%]	3.53–3.73
>24 days		3611 [7.15%]	6.93–7.38		4812 [3.41%]	3.32–3.51
Missing		0			0	
ASA physical status						
1		34,708 [68.75%]	68.34–69.15		110,077 [78.02%]	77.80–78.24
2		11,280 [22.34%]	21.98–22.71		22,982 [16.29%]	16.10–16.48
3		2989 [5.92%]	5.72–6.13		5448 [3.86%]	3.76–3.96
4		217 [0.38%]	0.38–0.49		369 [0.26%]	0.23–0.29
5		7 [0.01%]	0.00–0.02		32 [0.02%]	0.01–0.03
6		16 [0.03%]	0.02–0.05		41 [0,03%]	0.02–0.04
Missing		1267 [2.51%]	2.38–2.65		2133 [1.51%]	1.45–1.57
Ten most common indications for anaesthesia						
1	Tonsillectomy	5399 [10.69%]	10.42–10.96	Arm fracture	9158 [6.49%]	6.36–6.62
2	Head MRI	1918 [3.80%]	3.64–3.97	Tonsillectomy	8508 [6.03%]	5.91–6.16
3	Hernia repair	1774 [3.51%]	3.35–3.67	Appendicectomy	6585 [4.67%]	4.56–4.78
4	Arm fracture	1680 [3.33%]	3.18–3.49	Removal of osteosynthetic material	4298 [3.05%]	3.96–3.14
5	Testicular torsion	1450 [2.87%]	2.73–3.02	Phimosis	3534 [2.50%]	2.42–2.58
6	MRI other	1088 [2.16%]	2.04–2.29	Ear drum repair	2880 [2.04%]	1.97–2.12
7	Phimosis	1056 [2.09%]	1.97–2.22	Testicular torsion	2533 [1.80%]	1.73–1.87
8	Shoulder fracture	826 [1.64%]	1.53–1.75	Gastroscopy	2497 [1.77%]	1.70–1.84
9	Ear drum repair	814 [1.61%]	1.50–1.72	Lower leg soft tissue surgery	2367 [1.68%]	1.61–1.75
10	Strabismus surgery	571 [1.13%]	1.04–1.23	Termination of pregnancy	2365 [1.68%]	1.61–1.75
Missing		0			0	

1 = Days at hospital within the last 6 months before time of anaesthesia.

 © 2018 Association of Anaesthetists

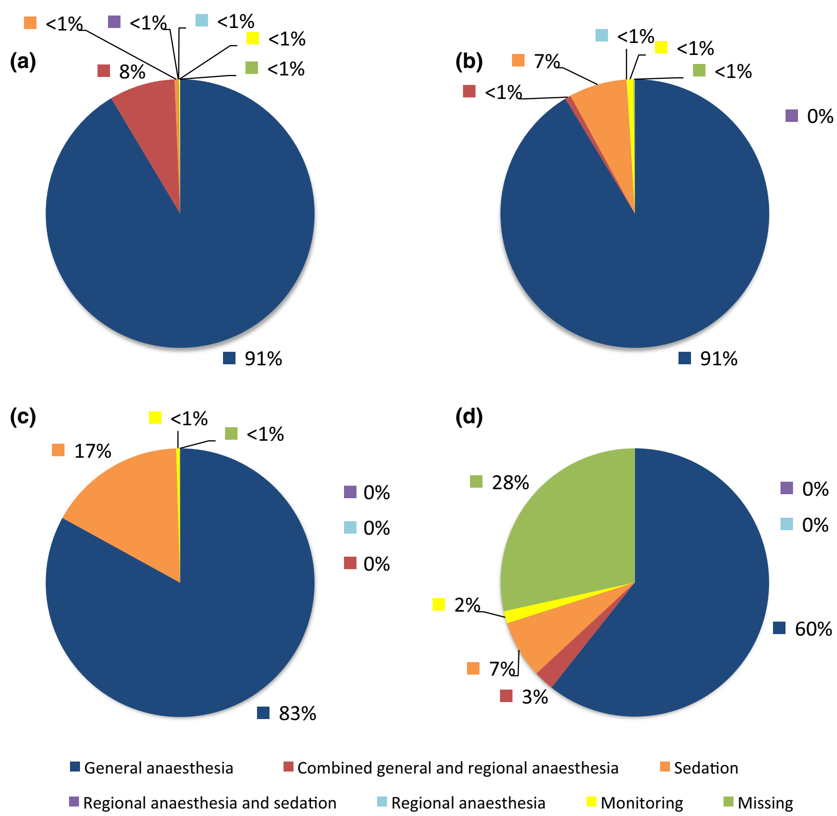

Figure 1 Method of anaesthesia used in children aged 2–5 years in Denmark between 2005 and 2015. In total, children aged 2–5 years received 50,484 cases of anaesthesia. The different types of anaesthesia methods are presented by reason for which anaesthesia was provided, and is grouped into four sub-groups: (a) surgery, (b) non-surgical care, (c) diagnostic radiology and (d) other reasons. Values are proportion.

Neuromuscular blocking drugs were used in 5722 out of 17,509 tracheal intubations (32.68%, 95%CI 31.99–33.38) for children aged 2–5 years and in 26,570 out of 52,444 tracheal intubations (50.66%, 95%CI 50.23–51.09) for children aged 6–17 years. The choice of neuromuscular blocking drugs in children aged 2–5 years compared with children aged 6–17 years was: non-depolarising agents 3142 (54.91%, 95%CI 53.62–56.20) vs. 9416 (35.44%, 95% CI 34.87–36.02); depolarising agents 2387 (41.72%, 95%CI 40.45–43.00) vs. 13,133 (49.43%, 95%CI 48.83–50.03); and a combination of both 193 (3.37%, 95%CI 2.93–3.87) vs. 4021 (15.13%, 95%CI 14.70–15.57).

Regional anaesthesia was part of the anaesthetic management in 3085 anaesthesia cases (8.00%; 95%CI 7.73–8.27) in children aged 2–5 years and in 11,663 cases (9.00%; 95%CI 8.85–9.16) in children aged 6–17 years, most often combined with general anaesthesia. The most commonly performed neuroaxial block was caudal epidural in children aged 2–5 years and lumbar epidural in children aged 6–17 years. The most commonly performed peripheral nerve block was infraclavicular nerve block in children aged 2–5 years and popliteal nerve block in children aged 6–17 years. Choices of regional anaesthesia are presented in Table 3. The use of regional anaesthesia over time is presented in Fig. 6. In children aged 2–5 years, complications were observed in 1667 anaesthesia cases (3.30%, 95%CI 3.15–3.46) compared with 5246 cases (3.72%, 95%CI 3.62–3.82) in those aged 6–17 years. In children aged 2–5 years, two complications were reported in 26 cases (0.05%, 95%CI 0.03–0.07) and three complications were reported in one case (0.02%, 95%CI −0.01 to 0.12). In children aged 6–17 years, two complications occurred in 10 cases (0.07%, 95%CI 0.03–0.11) and three complications occurred in one case (0.007%, 95%CI −0.007 to 0.021). Thus, the total number of complications was 1695 in children aged 2–5 years and 5258 in those aged 6–17 years. In children aged 2–5 years, difficult tracheal intubation was reported in 1259 anaesthesia episodes (2.49%, 95%CI 2.36–2.63) compared with 3321 anaesthesia episodes (2.42%, 95%CI 2.34–2.50) in those aged 6–17 years. Cormack and Lehane scores were recorded in difficult tracheal intubation cases

© 2018 Association of Anaesthetists

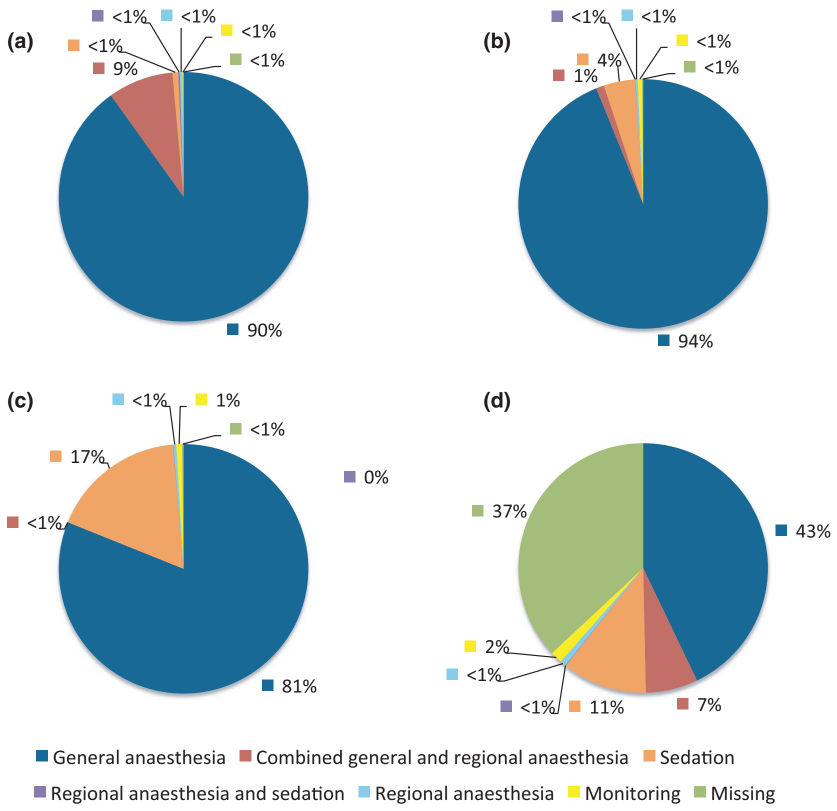

Figure 2 Method of anaesthesia used in children aged 6–17 years in Denmark between 2005 and 2015. The different types of anaesthesia methods are presented by reason for which anaesthesia was provided, and is grouped into four subgroups: (a) surgery, (b) non-surgical care, (c) diagnostic radiology and (d) other reasons. Values are proportion.

registered after 1 April 2008 [12]; there were 1229 cases (97.62%; 95%CI 96.62–98.33) in children aged 2–5 years and 2988 cases (89.97%; 95%CI 88.90–90.95) in those aged 6-17 years. In children aged 2–5 years, a Cormack and Lehane score of 3 was recorded in 35 cases (2.85%, 95%CI 2.06–3.94), a Cormack and Lehane score of 4 was recorded in four cases (0.33%, 95%CI 0.13–0.84) and scores were missing in 697 cases (56.71%; 95%CI 0.54–0.59). In children aged 6–17 years, a Cormack and Lehane score of 3 was observed in 77 cases (2.58%, 95%CI 2.07–3.21), a Cormack and Lehane score of 4 was observed in 32 cases (1.07%, 95%CI 0.76–1.51) and scores were missing in 2210 cases (73.76%; 95%CI 72.26–75.50). In the remaining cases, the children had Cormack and Lehane scores of 1 or 2.

Serious adverse events were observed in 15 anaesthesia cases (0.03%, 95%CI 0.02–0.05) in children aged 2–5 years compared with 32 cases (0.02%, 95%CI 0.01.0.03) in those aged 6–17 years. Complications are detailed in Table 4.

A certified anaesthesia specialist was involved in 37,988 anaesthesia cases (75.25%, 95%CI 74.87–75.62) in children aged 2–5 years compared with 78,422 cases (55.59%, 95%CI 55.33–55.85) in those aged 6–17 years. Trainees were involved in 5865 cases (11.62%; 95%CI 11.34–22.90) in children aged 2–5 years and in 15,300 cases (10.84%; 95%CI 10.68–11.00) in those aged 6–17 years. Nurse anaesthetists provided anaesthesia without the supervision of a physician in 3645 cases (7.22%, 95%CI 7.00–7.45) in children aged 2–5 years compared with 27,185 cases (19.27%; 95%CI 19.07–19.48) in those aged 6–17 years. No information on anaesthesia provider experience was recorded in 135 cases (0.27%, 95%CI 0.2–0.3) in children aged 2–5 years compared with 459 cases (0.33%, 95%CI 0.30–0.36) in those aged 6–17 years.

Missing data for baseline patient characteristics was minimal (Table 1). Data describing type of anaesthesia was missing in 222 cases (0.44%, 95%CI 0.39–0.50) in children aged 2–5 years compared with 589 cases (0.42%, 95%CI 0.39–0.46) in those aged 6–17 years. For airway management, data on the type of airway were missing in 2631 cases (5.43%, 95%CI 5.23–5.64) in children aged 2–5 years compared with 5392 cases

 © 2018 Association of Anaesthetists

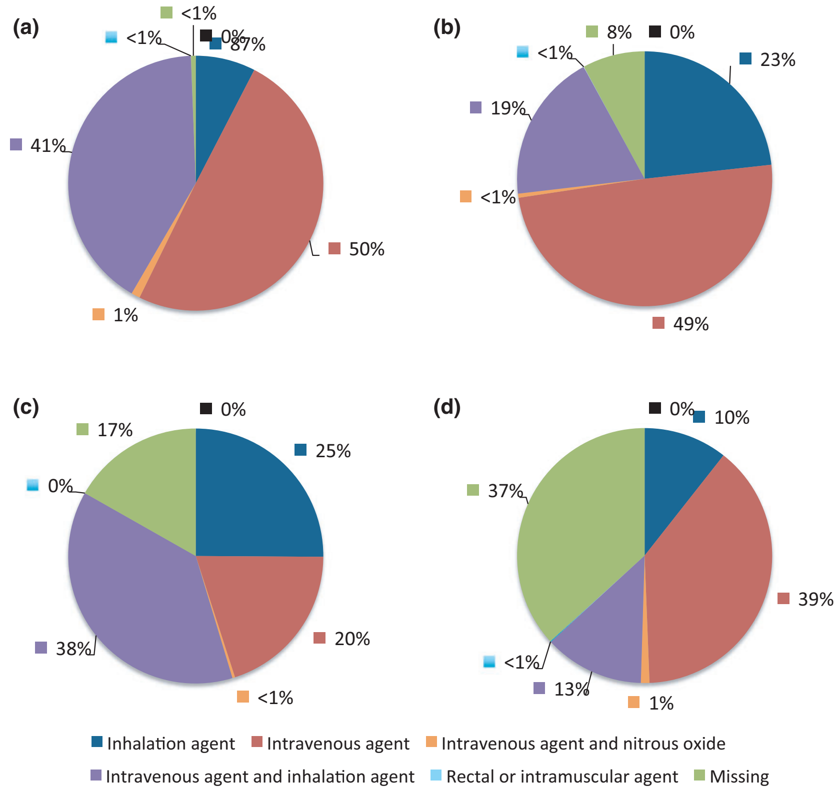

Figure 3 Type of anaesthetic agents used in children aged 2–5 years anaesthetised in Denmark between 2005 and 2015. The type of general anaesthesia agents are presented by reason for which anaesthesia was provided and is grouped into four sub-groups: (a) surgery, (b) non-surgical care, (c) diagnostic radiology and (d) other reasons. Values are proportion.

(3.93%; 95%CI 3.83.8–4.03) in those aged 6–17 years. For regional anaesthesia, additional data describing the method was missing in 639 cases (20.71%; 95%CI 19.32–22.18) in children aged 2–5 years and in 1922 cases (16.50%; 95%CI 15.84–17.19) in those aged 6–17 years (Table 3). The DAD reporting requirements were altered in 2008, when extra variables were made mandatory, and this resulted in considerably fewer missing data thereafter. Data on facemask ventilation was not included in the DAD before April 2008 and so the first years of data assessment did not have any information on this. After April 2008, details on facemask ventilation were missing in 565 cases (1.50%, 95%CI 1.38–1.63) in children aged 2–5 years compared with 887 cases (0.80%; 95%CI 0.75–0.85) in those aged 6–17 years. No peri-operative adverse event was reported in 10,982 cases (21.80%, 95%CI 21.44–22.16) in children aged 2–5 years or in 26,007 cases (18.40%; 95%CI 18.20–18.60) in those aged 6–17 years. Registration of adverse events was not a mandatory binary variable before April 2008.

Discussion

Our children aged 2–17 years undergoing anaesthesia were mostly of ASA physical status I. The younger children were more frequently anaesthetised at a university hospital, with non-surgical procedures and diagnostic radiology representing three times as many anaesthesia episodes in this age group compared with the older age group. For both age groups, general anaesthesia was the primary choice of anaesthesia. For surgery, general anaesthesia using inhalational agents in addition to i.v. agents, or alone, was more frequently used in the younger children, whereas the older children almost twice as commonly received total i.v. anaesthesia. Regional anaesthesia was part of the anaesthetic management in approximately 10% of cases for surgery in both groups, but peripheral nerve blocks were more commonly performed in older children. The use of regional anaesthesia increased slightly over time. Peri-operative complications, including serious adverse events, were rare.

The primary strength of this study was our use of prospectively collected data from continuously updated

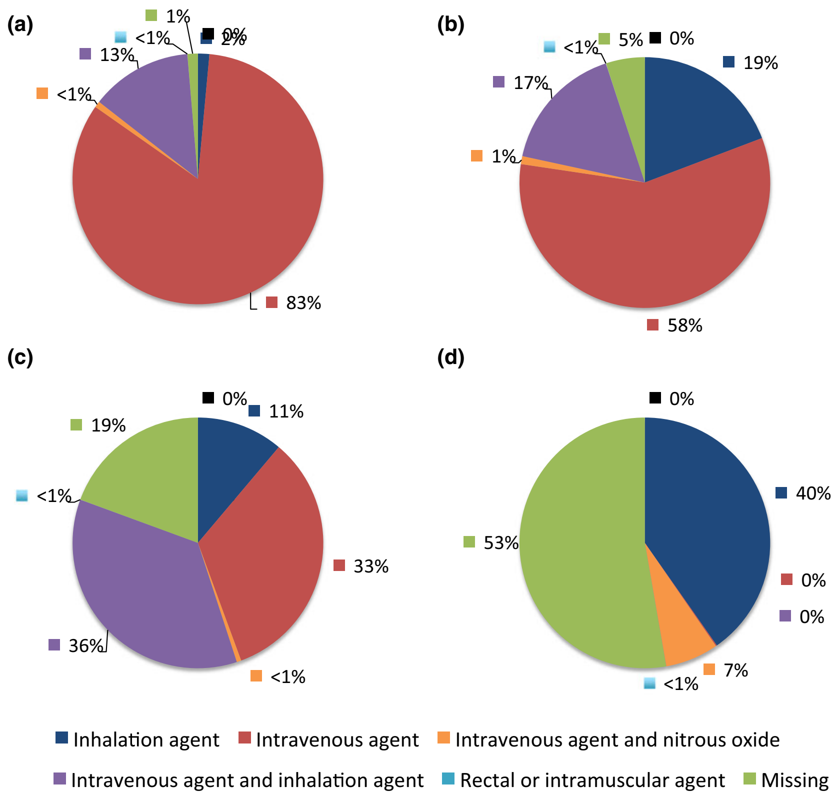

Figure 4 Type of anaesthetic agents used in children aged 6–17 years anaesthetised in Denmark between 2005 and 2015. The type of general anaesthesia agents are presented by reason for which anaesthesia was provided and is grouped into four sub-groups: (a) surgery, (b) non-surgical care, (c) diagnostic radiology and (d) other reasons. Values are proportion.

nationwide databases, which ensured a comprehensive sample with limited missing data. The study also had important limitations. First, the DAD was updated in 2008, which allowed enhanced capture of important information such as facemask ventilation and further stratification of complications. We encountered an information gap in these important parameters for anaesthesia episodes before update of the database. Based on the activity of institutions reporting to the DAD, the registry is believed to cover approximately 80% of anaesthesia episodes in Denmark. We may therefore have missed a large number of anaesthesia cases in this period. We cannot exclude selection bias among our study population. For example, it is possible that more healthy children received anaesthesia at private clinics, which do not report to DAD. In addition, the actual number of serious adverse events may be under-reported. We used criteria for serious adverse events that we believed unquestionably reflected events that threatened life or function, similar to the definition of adverse events in The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guideline (ICH-GCP) [18]. Many of the registered complications may have been serious, but we were unable to grade their severity because we had no access to individual patient files. Lastly, we were unable to address long-term events such as late cognitive disturbances because the observation period for data submitted to DAD is limited to patient discharge from the recovery area.

To our knowledge this study, together with our recently published data on children less than two years old [6], are the first to describe the practical management of paediatric anaesthesia on a nationwide basis. Compared with our study in children less than two years old [6], peri-operative complications occurred more frequently in this population. With increasing age, it was less likely that a certified anaesthesia specialist was involved in the anaesthetic management of the child. Within the current study design, we are not able to determine whether there is any causality between the competence of the anaesthesia provider and adverse events.

Previous studies have primarily described anaesthesia management for selected conditions or procedures, or

© 2018 Association of Anaesthetists

Table 2 Airway management in children aged 2–5 years and 6–17 years receiving general anaesthesia alone or in combination with regional anaesthesia in Denmark between 2005 and 2015. Values are number (proportion).

		95%CI for proportion
Type		
Facemask ventilation (exclusive)		
Age 2–5 years	7511 (15.50%)	15.18–15.82
Age 6–17 years	11,480 (8.36%)	8.21–8.51
Spontaneous breathing		
Age 2–5 years	3648 (7.53%)	7.30–7.77
Age 6–17 years	4029 (2.93%)	2.84–3.02
Supraglottic airway device		
Age 2–5 years	19,445 (40.13%)	39.69–40.57
Age 6–17 years	68,553 (49.91%)	49.65–50.17
Tracheal intubation[a]		
Direct laryngoscopy (maximum two attempts)		
Age 2–5 years	17,289 (35.68%)	35.25–36.11
Age 6–17 years	51,677 (37.62%)	37.36–37.88
Different techniques ± direct laryngoscopy (maximum two attempts)		
Age 2–5 years	92 (0.19%)	0.15–0.23
Age 6–17 years	496 (0.36%)	0.33–0.39
3 or more attempts (any method)		
Age 2–5 years	121 (0.25%)	0.21–0.30
Age 6–17 years	254 (0.18%)	0.16–0.20
Failed intubation		
Age 2–5 years	7 (0.01%)	0.00–0.02
Age 6–17 years	17 (0.01%)	0.01–0.02
Tracheostomy		
Age 2–5 years	0	0.00–0.01
Age 6–17 years	0	0.00–0.00
Missing data		
Age 2–5 years	341 (0.70%)	0.63–0.78
Age 6–17 years	857 (0.62%)	0.58–0.66
Ease of facemask ventilation[a]		
No attempt		
Age 2–5 years	11,713 (30.86%)	30.40–31.33
Age 6–17 years	32,619 (29.38%)	29.11–29.65
Easy		
Age 2–5 years	25,640 (67.56%)	67.09–68.03
Age 6–17 years	77,464 (69.78%)	69.51–70.05
Difficult		
Age 2–5 years	20 (0.05%)	0.03–0.08
Age 6–17 years	24 (0.02%)	0.01–0.03
Not defined		
Age 2–5 years	13 (0.03%)	0.02–0.05
Age 6–17 years	18 (0.02%)	0.01–0.03
Missing data		
Age 2–5 years	565 (1.49%)	1.37–1.62
Age 6–17 years	887 (0.80%)	0.75–0.85

[a]Results for ease of facemask ventilation are provided for anaesthetic episodes conducted after 1 April 2008 (n = 37,951 anaesthetic episodes in children 2–5 years and n = 111,012 anaesthetic episodes in children 6–17 years), when ease of facemask ventilation was added to the Danish Anaesthesia Database.

© 2018 Association of Anaesthetists

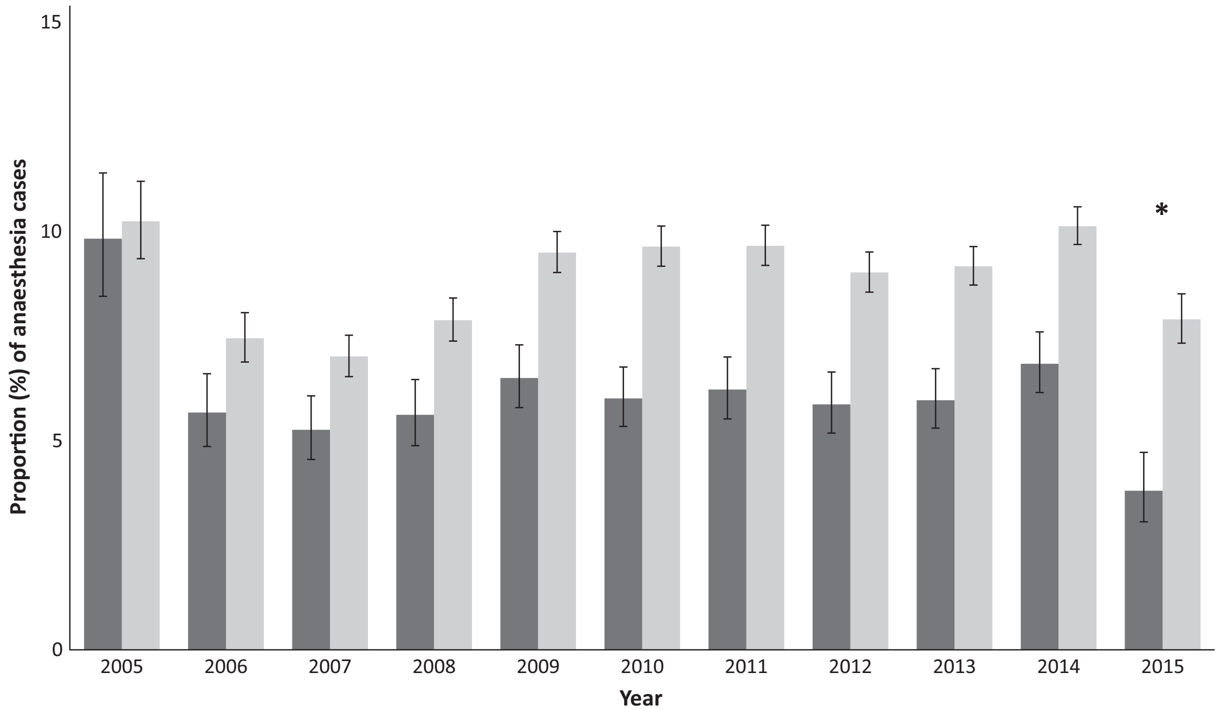

Figure 5 Use of regional anaesthesia for surgery in children aged 2-5 years and 6–17 years anaesthetised in Denmark between 2005 and 2015. Columns show the proportion of cases where regional techniques were employed and whiskers are 95% confidence intervals. *Data from 2015 are incomplete, because an updated version of the database was implemented in a stepwise fashion at Danish hospitals from February 1st 2015 and data were retrieved from the earlier version. ■ age 2–5; ■ age 6–17. [Correction added on 1 November 2018, after first online publication: The figure legend has been amended].

have focused on the incidence of adverse events in relation to anaesthesia [19–22]. Our findings revealed that provision of neuraxial anaesthesia and peripheral nerve blocks were rare. The widespread implementation of ultrasound may increase peripheral nerve block provision in the future, but more research on postoperative pain control utilising peripheral nerve blocks and catheters in children is warranted. Regional anaesthetic techniques have good safety profiles [23, 24], but whether these facilitate better care and improve outcomes in paediatric patients is uncertain [25, 26]. High-quality studies comparing outcomes in children receiving general anaesthesia compared with regional anaesthesia are needed. Concerns regarding potential impairment of postoperative cognitive development after exposure to general anaesthesia have arisen from animal studies, where administration of anaesthetic agents during synaptogenesis or rapid brain growth has been associated with neuronal apoptosis and neurodegeneration, and subsequent learning and behavioural abnormalities [27, 28]. Retrospective studies have demonstrated associations between exposure to anaesthetic drugs and cognitive dysfunction in infants and young children, which led the US Food and Drug Administration (FDA) to warn against lengthy or repeated use of general anaesthetics in children less than 3 years old [2, 29]. However, no synthesis of evidence from prospective, cohort or randomised trials is currently available to support the FDA warning [30]. Important factors such as emotional and social well-being, and physical health are likely to be more important in relation to long-term neurocognitive outcomes [31].

Total i.v. anaesthesia was predominantly provided to older children. In comparison, general anaesthesia for the younger children primarily consisted of inhalational agents alone or in combination with i.v. agents. Administration of inhalational anaesthetics does not require i.v. access, and can be used for children with needle phobia. It may be more difficult to predict interindividual pharmacokinetic and pharmacodynamic variability for i.v. agents [32], and safety concerns in children, such as propofol infusion syndrome during lengthy procedures, still exists [32]. In contrast, an observational study suggested that total i.v. anaesthesia reduces airway responsiveness [19] and a systematic review of 16 randomised clinical trials (that included 900 day surgery patients) suggested that, compared with sevoflurane, i.v. anaesthesia could minimise complications

 © 2018 Association of Anaesthetists

Table 3 Type of regional anaesthesia provided for surgery in children aged 2–5 years and 6–17 years anaesthetised in Denmark between 2005 and 2015. Values are number (proportion).

		Age group			
		2–5 years old		6–17 years old	
			95%CI		95%CI
Neuraxial block	Epidural, cervical	1 (0.03%)	0.01–0.18	8 (0.07%)	0.04–0.14
	Epidural, thoracic	21 (0.68%)	0.45–1.04	489 (4.19%)	3.84–4.57
	Epidural, lumbar	140 (4.54%)	3.86–5.33	582 (4.99%)	4.61–5.40
	Epidural, caudal	348 (11.28%)	10.21–12.44	73 (0.63%)	0.50–0.79
	Spinal, thoracic	0 (0.00%)	0.00–0.12	5 (0.04%)	0.02–0.10
	Spinal, lumbar	18 (0.58%)	0.37–0.92	235 (2.01%)	1.77–2.28
	Combined spinal/epidural	5 (0.16%)	0.07–0.38	31 (0.27%)	0.19–0.38
	Total number of neuraxial blocks	533 (17.28%)	15.99–18.65	1423 (12.20%)	11.62–12.81
i.v. regional block	Biers block	6 (0.19%)	0.09–0.42	40 (0.34%)	0.25–0.46
Infiltration block	Wound infiltration	340 (11.02%)	9.96–12.17	1547 (13.26%)	12.66–13.89
	Local anaesthesia for hernia repair	479 (15.53%)	14.29–16.85	388 (3.33%)	3.02–3.67
	Superficial infiltration	5 (0.16%)	0.07–0.38	18 (0.15%)	0.09–0.24
	Total number of infiltration blocks	824 (26.71%)	25.18–28.30	1953 (16.75%)	16.08–17.44
Peripheral nerve block	Axillary nerve block	66 (2.14%)	1.69–2.71	353 (3.03%)	2.73–3.36
	Femoral nerve block	65 (2.11%)	1.66–2.68	167 (1.43%)	1.23–1.66
	Ankle compartment block	17 (0.55%)	0.34–0.88	114 (0.98%)	0.82–1.18
	Intercostal nerve block	3 (0.10%)	0.03–0.29	17 (0.15%)	0.09–0.24
	Sciatic nerve block	17 (0.55%)	0.34–0.88	137 (1.17%)	0.99–1.38
	Median nerve block	2 (0.06%)	0.02–0.23	7 (0.06%)	0.02–0.12
	Obturator nerve block	0	0.00–0.12	92 (0.79%)	0.64–0.97
	Paravertebral nerve block	0	0.00–0.12	7 (0.06%)	0.02–0.12
	Radial nerve block	3 (0.10%)	0.03–0.29	21 (0.18%)	0.12–0.28
	Interscalene brachial plexus block	26 (0.84%)	0.57–1.23	355 (3.04%)	2.74–3.37
	Supraclavicular brachial plexus block	52 (1.69%)	1.29–2.21	221 (1.89%)	1.66–2.15
	'three in one' nerve block	0	0.00–0.12	4 (0.03%)	0.01–0.09
	Ulnar nerve block	7 (0.23%)	0.11–0.47	27 (0.23%)	0.16–0.33
	Wrist block	5 (0.16%)	0.02–0.38	2 (0.02%)	0.01–0.07
	Paracervical nerve block	0	0.00–0.12	1 (0.01%)	0.00–0.05
	Popliteal nerve block	87 (2.82%)	2.29–3.47	1012 (8.68%)	8.18–9.20
	Infraclavicular brachial plexus block	212 (6.87%)	6.03–7.82	748 (8.68%)	8.18–9.20
	Fascia iliaca block	7 (0.23%)	0.11–0.47	19 (0.16%)	0.10–0.25
	Psoas compartment block	0	0.00–0.12	3 (0.03%)	0.01–0.08
	Total number of peripheral nerve blocks	569 (18.44%)	17.11–19.85	4840 (41.50%)	40.61–42.40
Other block	Block not defined	514 (16.66%)	15.39–18.02	1485 (12.73%)	12.14–13.35
	Total number of other blocks	514 (16.66%)	15.39–18.02	1485 (12.73%)	12.14–13.35
Missing data		639 (20.71%)	19.32–22.18	1922 (16.48%)	15.82–17.16

such as postoperative nausea and vomiting and emergence agitation in children [33]. This is important because the incidence of postoperative nausea and vomiting in children older than 3 years is double that in adults [34]. However, the overall quality of evidence was regarded as poor due to a high risk of bias with the trials.

We observed a large proportion of younger children who received anaesthesia for non-surgical reasons, such as MRI scans. General anaesthesia may be necessary to ensure the patient remains still [35], but employment of non-pharmacological measures may be sufficient in more cases than previously anticipated. Alternative techniques

© 2018 Association of Anaesthetists

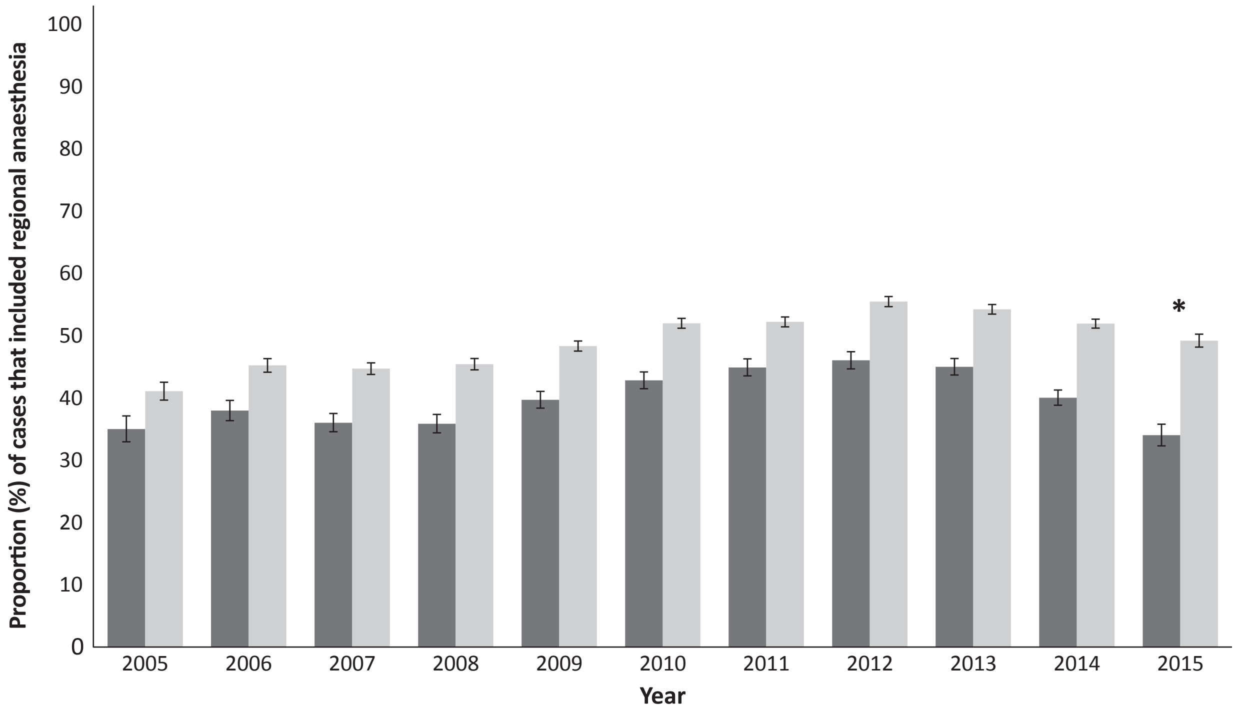

Figure 6 Use of supraglottic airway in children aged 2–5 years and 6–17 years anaesthetised in Denmark between 2005 and 2015. Columns show the proportion of cases where a supraglottic airway was employed and whiskers are 95% confidence intervals. *Data from 2015 are incomplete, because an updated version of the database was implemented stepwise at Danish hospitals from February 1st 2015 and data was retrieved from the earlier version. ■ age 2–5; ■ age 6–17. [Correction added on 1 November 2018, after first online publication: The figure legend has been amended].

for preparing children for minor procedures are available, such as distraction methods or hypnosis. A recent cross-sectional study found that children with moderate to severe pain seldom had a documented pain assessment, and neither evidence-based pharmacological nor 'non-pharmacological' techniques were regularly administered to control pain [36].

Serious adverse events were observed in less than 0.3% of anaesthesia cases in our study. The APRICOT study, which prospectively collected data in children aged 0–15 years from European institutions, found a 5.2% incidence of severe critical events [22]. The authors defined a severe critical event to be any respiratory, cardiac, allergic or neurological complication requiring immediate intervention which led, or may have led, to major disability and/or death. In comparison, we used a much narrower definition. Our results matched findings from similar database-driven studies [37, 38], which might indicate that database-driven studies are prone to underestimate the incidence of complications due to missing data or under-reporting of events. A 2014 study using the American Anaesthesia Safety Database reported an incidence of severe critical events of 0.1% among children [39], which was slightly lower than our findings.

International collaborations have been established to distribute principles for safe conduct of paediatric anaesthesia. The Safe-tots initiative advocates the application of five important principles when providing anaesthesia in children younger than 3 years old; that is, involvement of a paediatric anaesthesia specialist, centralised care, patients with special requirements should be anesthetised in dedicated paediatric centres, elective procedures should be optimally timed and peri-operative factors that compromise a patient's well-being should be avoided [5]. We observed that anaesthesia specialists were involved in 75% of anaesthesia episodes in children aged 2–5 years, and just over 50% of anaesthesia episodes in those aged 6–17 years. We are not aware of similar initiatives guiding safe conduct of anaesthesia for older children. Child age is inversely correlated with the risk of adverse peri-operative events [22], but the optimal strategy for practical peri-operative anaesthesia in older age groups remains to be determined, including at what stage the child can be treated the same as an adult.

 © 2018 Association of Anaesthetists

Table 4 Peri-operative complications in children aged 2–5 years and 6–17 years anaesthetised in Denmark between 2005 and 2015. Values are number (proportion).

		OT	Recovery area	Total	95%CI
Airway	Aspiration				
	Age 2–5 years	8 (0.16%)	2 (0.04%)	10 (0.20%)	0.08%–0.32%
	Age 6–17 years	28 (0.20%)	3 (0.02%)	31 (0.22%)	0.14%–0.30%
	Dental injury				
	Age 2–5 years	2 (0.04%)	0	2 (0.04%)	0.00%–0.09%
	Age 6–17 years	7 (0.05%)	0	7 (0.05%)	0.01%–0.09%
	Prolonged neuromuscular blockade with depolarising agent				
	Age 2–5 years	0 (0.00%)	0	0	0.00%–0.00%
	Age 6–17 years	2 (0.01%)	0	2 (0.01%)	0.00%–0.03%
	Difficulties in tracheal intubation				
	Age 2–5 years	1259 (24.9%)	0	1259 (24.9%)	23.6%–26.3%
	Age 6–17 years	3321 (23.5%)	0	3321 (23.5%)	22.7%–24.3%
	CICO				
	Age 2–5 years	9 (0.18%)	0	9 (0.18%)	0.06%–0.29%
	Age 6–17 years	17 (0.12%)	0 (0.00%)	17 (0.12%)	0.06%–0.18%
Respiratory	Respiratory insufficiency				
	Age 2–5 years	27 (0.53%)	24 (0.48%)	51 (1.01%)	0.73%–1.29%
	Age 6–17 years	25 (0.18%)	44 (0.31%)	69 (0.49%)	0.37%–0.60%
	Pneumothorax				
	Age 2–5 years	0 (0.00%)	1 (0.02%)	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	0 (0.00%)	9 (0.06%)	9 (0.06%)	0.02%–0.11%
	Pulmonary oedema				
	Age 2–5 years	0	0	0	0.00%–0.00%
	Age 6–17 years	0	0	0	0.00%–0.00%
Cardiac	CVC misplacement				
	Age 2–5 years	1 (0.02%)	0	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	2 (0.01%)	0	2 (0.01%)	0.00%–0.03%
	Cardiac arrest				
	Age 2–5 years	4 (0.08%)	0	4 (0.08%)	0.00%–0.16%
	Age 6–17 years	5 (0.04%)	3 (0.02%)	8 (0.06%)	0.02%–0.10%
	Death				
	Age 2–5 years	1 (0.02%)	0	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	5 (0.04%)	2 (0.01%)	7 (0.05%)	0.01%–0.09%
Central and peripheral nerve system	Insufficient regional anaesthesia				
	Age 2–5 years	1 (0.02%)	N/A	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	4 (0.03%)	8 (0.06%)	12 (0.09%)	0.04%–0.13%
	Nerve damage due to positioning				
	Age 2–5 years	1 (0.02%)	0	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	7 (0.05%)	18 (0.13%)	25 (0.18%)	0.11%–0.25%
	Awareness during surgery				
	Age 2–5 years	0	0	0	0.00%–0.00%
	Age 6–17 years	1 (0.01%)	4 (0.03%)	5 (0.04%)	0.00%–0.07%

(continued)

© 2018 Association of Anaesthetists

Table 4 (*continued*)

		OT	Recovery area	Total	95%CI
	Dural puncture				
	Age 2–5 years	0	0	0	0.00%–0.00%
	Age 6–17 years	2 (0.01%)	0	2 (0.01%)	0.00%–0.03%
	Pain (VAS > 5)				
	Age 2–5 years	3 (0.06%)	134 (2.65%)	137 (2.71%)	2.26%–3.17%
	Age 6–17 years	10 (0.7%)	837 (5.93%)	847 (6.0%)	5.60%–6.41%
Allergy	Anaphylaxis				
	Age 2–5 years	3 (0.06%)	0	3 (0.06%)	0.00%–0.13%
	Age 6–17 years	7 (0.05%)	4 (0.03%)	11 (0.08%)	0.03%–0.12%
	Pruritus				
	Age 2–5 years	0	2 (0.04%)	2 (0.04%)	0.00%–0.09%
	Age 6–17 years	0	37 (0.26%)	37 (0.26%)	0.18%–0.35%
Other peri-operative	Malignant hyperthermia				
	Age 2–5 years	0	N/A	0	0.00%–0.00%
	Age 6–17 years	0	N/A	0	0.00%–0.00%
	Disruption of anaesthesia				
	Age 2–5 years	7 (0.14%)	N/A	7 (0.14%)	0.04%–0.24%
	Age 6–17 years	9 (0.06%)	N/A	9 (0.06%)	0.02%–0.11%
	Medication error				
	Age 2–5 years	2 (0.04%)	1 (0.02%)	3 (0.06%)	0.00%–0.13%
	Age 6–17 years	6 (0.04%)	6 (0.04%)	12 (0.09%)	0.04%–0.13%
	Seizure				
	Age 2–5 years	0	0	0	0.00%–0.00%
	Age 6–17 years	3 (0.02%)	4 (0.03%)	7 (0.05%)	0.01%–0.09%
	Apparatus failure				
	Age 2–5 years	3 (0.06%)	1 (0.02%)	4 (0.08%)	0.00%–0.16%
	Age 6–17 years	12 (0.09%)	0 (0.00%)	12 (0.09%)	0.04%–0.13%
Other postoperative	Urinary retention				
	Age 2–5 years	0	22 (0.44%)	22 (0.44%)	0.25%–0.62%
	Age 6–17 years	1 (0.01%)	570 (4.04%)	571 (4.05%)	3.72%–4.38%
	Postoperative nausea and vomiting				
	Age 2–5 years	1 (0.02%)	72 (1.43%)	73 (1.45%)	1.11%–1.78%
	Age 6–17 years	1 (0.01%)	8 (0.06%)	9 (0.06%)	0.02%–0.11%
	Hypothermia				
	Age 2–5 years	0	1 (0.02%)	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	0	7 (0.05%)	7 (0.05%)	0.01%–0.09%
	Eye injury				
	Age 2–5 years	0	1 (0.02%)	1 (0.02%)	0.00%–0.06%
	Age 6–17 years	0	2 (0.01%)	2 (0.01%)	0.00%–0.03%
Not defined	Other				
	Age 2–5 years	82 (1.62%)	20 (0.40%)	102 (2.02%)	1.63%–2.41%
	Age 6–17 years	107 (0.76%)	110 (0.80%)	217 (1.54%)	1.33%–1.74%
Total number of complications	Age 2–5 years			1667 (33.0%)	31.5%–34.6%
	Age 6–17 years			5246 (37.2%)	36.2%–38.2%
Missing data	Age 2–5 years			10,982 (2.18%)	2.14%–22.1%
	Age 6–17 years			26,007 (1.84%)	1.82%–1.86%

OT, operating theatre; CICO, cannot intubate cannot oxygenate; CVC, central venous catheter; N/A, not applicable.

 © 2018 Association of Anaesthetists

In conclusion, we believe this study provides important information on children aged 2–17 years undergoing anaesthesia in Denmark from 2005 to 2015. We found that younger children (aged 2–5 years) compared with older children (aged 6–17 years) were more frequently anaesthetised for non-surgical reasons, at a university hospital and using inhalational agents. Overall, complications were rare.

Acknowledgements

We thank staff working at The Danish Anaesthesia Database and at the participating departments who collected data. No external funding or competing interests declared.

References

1. Arlachov Y, Ganatra RH. Sedation/anaesthesia in paediatric radiology. *British Journal of Radiology* 2012; **85**: e1018–31.
2. Ing C, DiMaggio C, Whitehouse A, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; **130**: e476–85.
3. Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 2009; **110**: 796–804.
4. Hansen TG, Pedersen JK, Henneberg SW, et al. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. *Anesthesiology* 2011; **114**: 1076–85.
5. Weiss M, Vutskits L, Hansen TG, Engelhardt T. Safe anesthesia for every tot – the SAFETOTS initiative. *Current Opinion in Anaesthesiology* 2015; **28**: 302–7.
6. Strøm C, Afshari A, Lundstrøm LH, Lohse N. Characteristics of children less than 2 years of age undergoing anaesthesia in Denmark 2005–2015: a national observational study. *Anaesthesia* 2018; **73**: 1195–1206.
7. Danish Health Authority. Specialised hospital services – anaesthesiology (paper in Danish). https://www.sst.dk/da/planlaegning/specialeplanlaegning/gaeldende-specialeplan/anaestesiologi (accessed 01/05/2017).
8. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7.
9. Antonsen K, Rosenstock CV, Lundstrøm LH. The danish anaesthesia database. *Clinical Epidemiology* 2016; **8**: 435–8.
10. Pedersen CB. The danish civil registration system. *Scandinavian Journal of Public Health* 2011; **39**: 22–5.
11. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The danish national hospital register. A valuable source of data for modern health sciences. *Danish Medical Bulletin* 1999; **46**: 263–8.
12. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–11.
13. Lunde AS, Lundeborg S, Lettenstrom GS, Thygesen L, Huebner J. The person-number systems of Sweden, Norway, Denmark, and Israel. *Vital and Health Statistics. Series 2, Data Evaluation and Methods Research* 1980; **84**: 1–59.
14. World Health Organization. International statistical classification of diseases and health related problems. 2004. http://www.who.int/classifications/icd/en/ (accessed 01/01/2017).
15. NOMESCO. Classification of Surgical Procedures (NCSP). http://www.nordclass.se/ncsp_e.htm (accessed 19/02/2017).
16. American Society of Anesthesiologists. ASA physical status classification system. https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system (accessed 08/04/2017).
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987; **40**: 373–83.
18. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Guidelines for good clinical practice. http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html (accessed 08/04/2017).
19. von Ungern-Sternberg BS, Boda K, Chambers NA, et al. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. *Lancet* 2010; **376**: 773–83.
20. Mamie C, Habre W, Delhumeau C, Argiroffo CB, Morabia A. Incidence and risk factors of perioperative respiratory adverse events in children undergoing elective surgery. *Pediatric Anesthesia* 2004; **14**: 218–24.
21. Murat I, Constant I, Maud'huy H. Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. *Pediatric Anesthesia* 2004; **14**: 158–66.
22. Habre W, Disma N, Virag K, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respiratory Medicine* 2017; **5**: 412–25.
23. Jöhr M. Regional anaesthesia in neonates, infants and children. *European Journal of Anaesthesiology* 2015; **32**: 289–97.
24. Polaner DM, Taenzer AH, Walker BJ, et al. Pediatric regional anesthesia network (PRAN). *Anesthesia and Analgesia* 2012; **115**: 1353–64.
25. Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016; **387**: 239–50.
26. Bosenberg A. Benefits of regional anesthesia in children. *Pediatric Anesthesia* 2012; **22**: 10–18.
27. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *Journal of Neuroscience* 2003; **23**: 876–82.
28. Slikker W, Zou X, Hotchkiss CE, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. *Toxicological Sciences* 2007; **98**: 145–58.
29. Fda, Cder. FDA drug safety communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533346.htm (accessed 08/04/2017).
30. Sinner B, Becke K, Engelhard K. General anaesthetics and the developing brain: an overview. *Anaesthesia* 2014; **69**: 1009–22.
31. Hansen TG, Engelhardt T, Weiss M. The relevance of anesthetic drug-induced neurotoxicity. *JAMA Pediatrics* 2017; **171**: e163481.
32. Gaynor J, Ansermino JM. Paediatric total intravenous anaesthesia. *BJA Education* 2016; **16**: 369–73.
33. Ortiz AC, Atallah ÁN, Matos D, da Silva EM. Intravenous versus inhalational anaesthesia for paediatric outpatient surgery. In: Ortiz AC, ed. *Cochrane database of systematic reviews*. Chichester, UK: John Wiley and Sons Ltd, 2014.
34. Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. *Central Nervous System Drugs* 2015; **29**: 543–63.

© 2018 Association of Anaesthetists

35. Edwards AD, Arthurs OJ. Paediatric MRI under sedation: is it necessary? What is the evidence for the alternatives? *Pediatric Radiology* 2011; **41**: 1353–64.
36. Walther-Larsen S, Pedersen MT, Friis SM, et al. Pain prevalence in hospitalized children: a prospective cross-sectional survey in four Danish university hospitals. *Acta Anaesthesiologica Scandinavica* 2017; **61**: 328–37.
37. Bhananker SM, Ramamoorthy C, Geiduschek JM, et al. Anesthesia-related cardiac arrest in children: update from the pediatric perioperative cardiac arrest registry. *Anesthesia and Analgesia* 2007; **105**: 344–50.
38. Ahmed A, Ali M, Khan M, Khan F. Perioperative cardiac arrests in children at a university teaching hospital of a developing country over 15 years. *Pediatric Anesthesia* 2009; **19**: 581–6.
39. Kurth CD, Tyler D, Heitmiller E, Tosone SR, Martin L, Deshpande JK. National pediatric anesthesia safety quality improvement program in the United States. *Anesthesia and Analgesia* 2014; **119**: 112–21.

 © 2018 Association of Anaesthetists