Off-label use of dexmedetomidine in paediatric anaesthesiology: an international survey of 791 (paediatric) anaesthesiologists

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Abstract

The aim of this international study is to gain information on dexmedetomidine prescription by paediatric anaesthesiologists. We composed an online survey containing questions about the prescription rate of dexmedetomidine, administration route and dosage, adverse drug reactions, education on the drug and overall experience. Members of specialist paediatric anaesthesia societies of Europe (ESPA,n=849), New Zealand and Australia (SPANZA,n=320), Great Britain and Ireland (APAGBI,n=872) and the United States (SPA,n=3130) were e-mailed a link to this survey; responses were collected July and August 2019. Eight hundred and fifty-one invitees (851/5171,17%) responded, of whom 60 did not report their countries and were therefore excluded from the analyses. The ESPA members' response rate was 25%, SPANZA35%, APAGBI15% and SPA10%. Dexmedetomidine is prescribed by 70% of all respondents (ESPA 121/229,53%;SPANZA 77/111,69%;APAGBI 44/129,34% and SPA 310/322,96%) of whom 73% has access to mostly local protocols. Differences in the use were mainly found in the age of the patients receiving dexmedetomidine (SPA primarily <1 year, others primarily >1 year). Members of SPANZA, APAGBI and SPA had not noted adverse drug reactions, although 61% of ESPA members had noted bradycardia. The majority of SPA respondents were not aware of any contraindications, whereas members from all other societies were aware of these. Although an on-label paediatric indication and clinical evidence have yet been lacking, many anaesthesiologists use dexmedetomidine in paediatrics for premedication, procedural sedation, ICU sedation and anaesthesia. The large intercontinental differences in dexmedetomidine prescription call for consensus and worldwide education on the optimal use of dexmedetomidine in paediatric practice.

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Running head: Dexmedetomidine in paediatric anaesthesia

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What is already known about this subject: - Anaesthesiologists are searching for new neuroprotective drugs for general anaesthesia, of which dexmedetomidine might be one. - Due to its haemodynamic stability and absence of respiratory depressions, dexmedetomidine is increasingly prescribed off-label in children as premedication, for ICU sedation, procedural sedation and anaesthesia.

What this study adds: - In spite of its off-label status, dexmedetomidine is commonly used in paediatric practice all over the world, mainly for procedural sedation and as premedication for anaesthesia. - Ages of the patients receiving dexmedetomidine differ between continents. - Intercontinental sharing of experience is required to develop dosing recommendations, protocols and teaching opportunities for (procedural) sedation and anaesthesia with dexmedetomidine.

Abstract

Aim

The aim of this international study is to gain information on dexmedetomidine prescription by paediatric anaesthesiologists.

Methods

We composed an online survey containing questions about the prescription rate of dexmedetomidine, administration route and dosage, adverse drug reactions, education on the drug and overall experience. Members of specialist paediatric anaesthesia societies of Europe (ESPA,n=849), New Zealand and Australia (SPANZA,n=320), Great Britain and Ireland (APAGBI,n=872) and the United States (SPA,n=3130) were e-mailed a link to this survey; responses were collected July and August 2019.

Results

Eight hundred and fifty-one invitees (851/5171,17%) responded, of whom 60 did not report their countries and were therefore excluded from the analyses. The ESPA members' response rate was 25%, SPANZA35%, APAGBI15% and SPA10%. Dexmedetomidine is prescribed by 70% of all respondents (ESPA 121/229,53%;SPANZA 77/111,69%;APAGBI 44/129,34% and SPA 310/322,96%) of whom 73% has access to mostly local protocols. Differences in the use were mainly found in the age of the patients receiving dexmedetomidine (SPA primarily <1 year, others primarily >1 year). Members of SPANZA, APAGBI and SPA had not noted adverse drug reactions, although 61% of ESPA members had noted bradycardia. The majority of SPA respondents were not aware of any contraindications, whereas members from all other societies were aware of these.

Conclusions

Although an on-label paediatric indication and clinical evidence have yet been lacking, many anaesthesiologists use dexmedetomidine in paediatrics for premedication, procedural sedation, ICU sedation and anaesthesia. The large intercontinental differences in dexmedetomidine prescription call for consensus and worldwide education on the optimal use of dexmedetomidine in paediatric practice.

Introduction

Dexmedetomidine is increasingly used in children for premedication, sedation in the intensive care unit (ICU), procedural sedation, and anaesthesia, but also to prevent postoperative agitation, nausea and vomiting.[1,2] Dexmedetomidine is an alpha-2 adrenoceptor agonist that provides adequate sedation with facilitated arousal and analgesia without respiratory depression. Dexmedetomidine offers advantages over traditional anaesthetics for its hemodynamic stability, sedative properties and multimodal pain management.[3,4] Its colourless and odourless properties make it suitable for paediatric intranasal administration as premedication. Furthermore, dexmedetomidine ameliorates separation anxiety in children.[5,6]

Despite the lack of evidence and off-label use of dexmedetomidine for anaesthesia in patients younger than 18 years of age, the worldwide use of dexmedetomidine for paediatric anaesthesia is still increasing.[7,8] Experimental research has shown that dexmedetomidine may have a neuroprotective effect when co-administered with other anaesthetic medications.[9,10] However, evidence is lacking from clinical studies and randomized controlled trials on the short- and long-term effects of dexmedetomidine use in children undergoing general anaesthesia or receiving prolonged dexmedetomidine infusions. Multiple ongoing studies in children investigate the relationship between dexmedetomidine-based general anaesthesia and long-term neurodevelopmental outcomes.[4,11]

Furthermore, dosing protocols for children have not yet been published, and an international consensus on the use of dexmedetomidine in paediatrics is missing.[12-16] Incorrect application could lead to yet unknown adverse long-term effects. Therefore, overexposure to the drug should be avoided.

We postulated that dexmedetomidine is frequently used in paediatric anaesthesia without a structured implementation procedure including, for example, education and protocols, which leads to large application differences. We performed a survey of international paediatric anaesthesia specialist societies in order to gather information on the use of dexmedetomidine in children by paediatric anaesthesiologists worldwide and identify areas of future need for safe and effective use of dexmedetomidine in children.

Methods

We performed an online survey on the use of dexmedetomidine in paediatric anaesthesiology, starting July 16th 2019 and with closing date August 16th, 2019. The target response rate was 25%.

Survey respondents were recruited from the following societies for paediatric anaesthesiologists: European Society for Paediatric Anaesthesiology (ESPA), Society for Paediatric Anaesthesia in New Zealand and Australia (SPANZA), Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI), and Society for Paediatric Anesthesia (SPA). The boards of these societies were invited to distribute a survey, described below, amongst their members via an e-mail with a link to the survey. ESPA, APAGBI and SPA sent an e-mail with the link to the survey to all members. SPANZA mentioned the survey and link in a newsletter. ESPA and SPANZA sent a reminder one month later. APAGBI and SPA have email usage protocols for survey distribution in place, which do not provide for reminders.

Survey

Experts in the field of paediatric anaesthesia developed a 16-question survey to collect information on the use of dexmedetomidine in paediatric anaesthesiology care. The items addressed whether the respondent regularly prescribes dexmedetomidine to children, perceived barriers for the use of dexmedetomidine in practice, in what setting dexmedetomidine was used, the availability of a local protocol, how the respondent had been educated on dexmedetomidine in paediatrics, and clinical experiences with the drug, such as adverse events (survey in Supplementary Data).

The survey was designed to be completed anonymously within 10 minutes by every anonymous participant. It was delivered through Limesurvey (Limesurvey GmbH, Hamburg, Germany) secure web application for building and managing online surveys and databases.[17] The survey was tested among paediatric anaesthesiologists at the Erasmus MC-Sophia Children's Hospital Rotterdam. Following this test, some of the questions were adjusted for improvement.

Analysis

The survey data were exported from Limesurvey to Microsoft Excel Version 16.32 (Microsoft Corporation, Redmond, Washington, USA) and SPSS Statistics Version 24 (IBM Corporation, Armonk, NY, USA) to perform descriptive statistical analysis. SPSS was used to compare the groups and summarize the data. Due to the explorative nature of the study, no comparative statistics were performed.

Incomplete responses with at least 40% completion were still included for analysis. The numbers of respondents per question were determined in order to provide accurate response rates per question.

Responses of respondents who had not stated the country of practice were excluded from analysis because these responses could not be assigned to a societal group.

Questions asked regarding experience with adverse drug reactions were not specified as to whether these reactions were experienced once or that these were experienced more frequently.

Results

In total 5171 society members received an invitation (Figure 1). The number of anaesthesiologists who were members of multiple societies was unknown. Sixty respondents were excluded because the country of practice. The overall response was 17% and varied from 35% (SPANZA) to 10% (SPA) among the various societies (Table 1). Seventy-five incomplete surveys were included for analysis. No incomplete surveys were excluded due to >40% completion of the survey. Respondents who did not answer a specific question were left out of consideration regarding this question, as reflected in the Tables 1, 3 and 4. Across all societies, most respondents worked in a tertiary hospital as a full-time paediatric anaesthesiologist (693/791, 88%). Respondents had practised as a physician for a median duration of 12 years [IQR 6-21].

Almost all (96%) SPA respondents used dexmedetomidine in paediatric practice (310/322,), versus 69% of SPANZA respondents. ESPA respondents and APAGBI respondents did not use dexmedetomidine as often: 53% and 34%, respectively (Table 1).

Respondents who use dexmedetomidine

Overall, seventy percent of the respondents used dexmedetomidine in paediatric practice. A protocol was not available for members of ESPA (57/121, 47%) and SPANZA (33/77, 43%), whereas nearly all SPA members (285/310, 92%) had access to a protocol, as well as the majority of the APAGBI members (27/44, 61%). The drug was used for children of all ages: SPA members used dexmedetomidine mainly in patients younger than 1 year of age, whereas all other respondents used dexmedetomidine mainly in patients older than 1 year of age. Overall, dexmedetomidine was mostly used for procedural sedation (375/552, 68%), as reported by ESPA respondents (78/121, 65%) and SPA respondents (253/310, 82%). The main indication for members of SPANZA (62/77, 81%) and members of APAGBI (30/44, 68%) was premedication.

Broad ranges of dosages were reported for the use of dexmedetomidine for different applications (Table 2). For premedication, the most frequently used dose was 2.0 ug/kg intranasal bolus administration. For procedural sedation, intensive care sedation, anaesthesia and postoperative analgesia an intravenous infusion was the most frequently used route of administration. Dosages for intravenous administration differed widely (Table 2). Oral and intramuscular administration were reported as well.

The arguments to start using dexmedetomidine in paediatric practice were fewer cases of emergence delirium compared to traditionally used anaesthetics (273/552, 50%), and fewer respiratory complications (222/552, 40%). The SPA respondents mainly reported fewer emergence delirium cases (143/310, 46%), the ESPA respondents fewer respiratory complications (79/121, 65%). The APAGBI respondents (24/44, 55%) and SPANZA respondents (49/77, 64%) mainly reported a good profile for premedication (Figure 2). Few respondents had started using dexmedetomidine for its opioid sparing effect. Fifty-six respondents reported they had received specific training or training though a protocol. Others had individually consulted relevant literature (n=98); had discussed the application with colleagues (n=79) or had learned to use dexmedetomidine via trial and error (n=50).

The most commonly observed adverse drug reactions were bradycardia (n=129) and nausea (n=99). However, many respondents from all societies (275/552, 50%) had not observed adverse drug reactions. Respondents from the SPA were not familiar with contraindications (286/310, 92%), but the majority of respondents from other societies (67%) were aware of contra-indications for the use of dexmedetomidine in paediatric care (Table 3).

Respondents who do not use dexmedetomidine

In total 206 of the 791 respondents (26%) did not use dexmedetomidine in paediatric care, mainly members of ESPA (90/229, 39%) and APAGBI (80/129, 62%) (Table 4). Most of them had not been educated in the use of dexmedetomidine (182/206, 88%), but were familiar with the drug (89/229, 49%). Lack of education was one of the main reasons not to use dexmedetomidine in paediatric practice (99/206, 48%). Other perceived barriers to using dexmedetomidine were the absence of local protocol (95/206, 46%), and no consensus among local staff (68/206, 33%) (Figure 3). Furthermore, for 46 of these 206 respondents (22%) the drug was not available; mainly reported by APAGBI respondents: 34/80, 43%) The majority of non-users (174/206, 85%) were willing to start using dexmedetomidine for premedication (126/174, 72%) and procedural sedation (133/174, 76%, Table 4). The most important reasons for the willingness to start using dexmedetomidine were the benefits (82/174, 47%) and the safer alternative to the currently used drugs (38/174, 22%). Reasons for not being willing to start using dexmedetomidine (29/206, 14%) were the availability of better alternatives (7/29, 24%), no need (9/27, 31%), and need for more individual and general experience with dexmedetomidine (7/29, 24%).

Discussion

This international survey revealed that despite the off-label use in children, dexmedetomidine is frequently used in paediatric anaesthesiology settings, even without the availability of national or local protocols. The main indications were premedication, procedural sedation and IC sedation. Most of the anaesthesiologists who used dexmedetomidine reported absence of adverse drug reactions, as well as awareness of contraindications for the use in paediatrics.

A prospective pilot study showed that dexmedetomidine-based anaesthesia creates satisfactory conditions for paediatric surgery.[4] Dexmedetomidine proved to be useful for various types of surgical procedures, such as airway procedures, neurosurgery, cardiac surgery and ambulatory procedures.[18] Dexmedetomidine has not been approved for use in paediatric care in any country worldwide, which would explain why structured education of paediatric anaesthesiologists on its use by manufacturers is lacking. Only 56 respondents (10%)who use dexmedetomidine had received such education. Most respondents did not have access to structured education and taught themselves by reading scientific papers, discussing with colleagues and/or were self-taught. Respondents from the SPA primarily used dexmedetomidine in patients younger than 1 year of age, whereas respondents from other societies mainly used it in patients older than 1 year of age. This discrepancy might be related to the interpretation of the 2016 FDA statement concerning the effects of anaesthesia on the young brain; i.e., children younger than 3 years of age.[19] Shortly thereafter, a consensus statement for European anaesthesiologists concluded that there was no compelling evidence to change anaesthetic practice, but that unnecessary procedures should be avoided.[20] These conflicting statements may have had effects on the change of current practice. Since anaesthesiologists in the USA have been warned for the effects on the young brain, it is likely that they would search for a less neurotoxic alternative to the traditional anaesthetics –and use this alternative in the young patients. This may also explain why respondents who do not use dexmedetomidine are willing to start using it as an alternative to the currently used anaesthetics, as dexmedetomidine is thought not to be neurotoxic and provides satisfying sedation. Other different indications reported by the respondents from the different societies cannot be explained by the issued warnings. SPANZA and APAGBI members used dexmedetomidine mainly for premedication, whereas ESPA and SPA members used it mainly for procedural sedation. In the present survey study, the opioid-sparing effect was another reason for some anaesthesiologists to start using dexmedetomidine in paediatric practice. Administration of dexmedetomidine intraoperatively has been associated with a lesser need for postoperative analgesia and a lesser need for fentanyl intraoperatively.[21-24]

Our survey showed that dosing regimens for paediatric care differ widely. Studies describing the pharmacokinetics of dexmedetomidine indicate that children would require a higher dosage per kg bodyweight compared to adults to achieve comparable exposure, due to a larger volume of distribution in children.[25] A previous study described the off-label use of dexmedetomidine in paediatric care within the European Union (EU), indicated for ICU sedation, anaesthesia and procedural sedation.[7] In the EU, a maximum infusion rate of 1.4μg*kg^{-1}*h^{-1} is approved for adult sedation; however, a recently published study in Europe showed that infusion rates exceeding 1.4μg*kg^{-1}*h^{-1} were used in 11% of children.[7] Our study shows a similar practice: reported infusion rates ranged from 0.1 μg*kg^{-1}*h^{-1} to 3.0 μg*kg^{-1}*h^{-1}. Dosing seems to vary inter-individually, especially in paediatrics, as shown by variable half-life and clearance.[26] Furthermore, the dosing regimen depends on the route of administration. For nasal administration, a 2 μg*kg^{-1} dose was the most commonly used premedication dose in the present study. Therefore, various dosing regimens should be available for physicians to use.

Bradycardia and hypotension were the most frequently reported side effects of dexmedetomidine. Generally, these side effects do not require additional treatment.[15] Interestingly, only SPA respondents reported an adverse drug reaction, nausea. A meta-analysis has shown that dexmedetomidine prevents postoperative nausea and vomiting in children and in adults when administered during general anesthesia.[27] The SPA respondents mostly use dexmedetomidine in patients younger than 1 year of age, and respondents from the other societies mostly in patients above 1 year of age, which might explain the difference in reported adverse drug reactions.[28]

Dexmedetomidine is not the only anaesthetic drug used off-label in paediatric anaesthesiology. Other studies have found that most drugs administered to induce and to maintain anaesthesia are off-label.[29] Our study confirmed that dexmedetomidine is used in infants, the age group with the least number of drugs licenced for use.[30] In a previous study, patients treated with off-label drugs had a significantly higher risk of adverse drug reactions.[31] As we should not expose children to unnecessary risks, it is important to investigate the pharmacokinetics and pharmacodynamics of new drugs in clinical trials in the paediatric population.[32] In the absence of trials, formal education for those prescribing and administering dexmedetomidine to children would be necessary.

Our survey revealed various barriers to the use of dexmedetomidine in paediatric practice. The main barriers were the price of dexmedetomidine, non-availability of the drug, the lack of knowledge, and the lack of education. Introduction of new drugs or adjusted use of drugs in anaesthesia rarely comes with education of the anesthesiologists.[33] However, bed-side teaching of an anaesthesiologist with experience (local opinion leader) in use of dexmedetomidine during anaesthesia could counteract this barrier, because this is an intervention for successful implementation[34,35] Unfortunately, our survey did not investigate the reason why the lack of training has such a negative effect on the use of dexmedetomidine, specifically. Mainly respondents from the APAGBI reported not to have access to dexmedetomidine, which explains the low use amongst APAGBI members. This might be due to the fact that dexmedetomidine has not been licensed for anaesthesia in the UK.[36,37] Another reason why respondents do not use dexmedetomidine is that they lack information about the drug. Long-term effects on the use of dexmedetomidine in children have not yet been published no studies have been published on the. Studies have focussed on the short-term effects, such as safety of administration, emergence delirium, postoperative nausea and vomiting.[38]Dexmedetomidine pharmacodynamics and pharmacokinetics have mainly been described for adult populations.[15]

The use of dexmedetomidine amongst respondents from different societies clearly differed with regard to patient age categories, routes of administration, bodyweight-based dosages, dosing regimens and the availability of protocols. We argue that paediatric anaesthesiologists from different societies must learn from the others' experiences, share information, and ultimately reach consensus on the optimal dexmedetomidine therapy in paediatric anaesthesia. Such consensus might stimulate good use. Consensus could be reached by evidence, expert interpretation and experience. This consensus would lead to fewer differences in drug prescriptions amongst hospitals, leading to improved patient safety.[39] This consensus should also include adverse drug reactions and provide an option to report experienced adverse drug events for pharmacovigilance.

We hypothesise that the unproven neurotoxicity of currently used anaesthetics reduces the need for introduction of new drugs. The lack of evidence on the advantages of dexmedetomidine does not provide a reason to change current practice by introducing a new off-label drug with unknown short-term and long-term risks.

Although we reached out to four major societies and associations for paediatric anaesthesiologists, we could not reach all paediatric anaesthesiologists because not everybody is a member of one of these societies. We probably missed a large proportion, primarily those working in Asia, Africa and South America.[40] E-mails with a link to the survey were sent out by the societies themselves, on different dates after July 16$^{\text{th}}$, 2019. The closing date was the same for all societies: August 16$^{\text{th}}$. The different time windows to respond to the survey could have led to response bias. We acknowledge the responder and non-responder bias for this survey, which could have influenced the results. Those who do not use dexmedetomidine in paediatrics might have been less likely to participate, since they do not have any benefits from participation in the study. The target response rate was set on 25%, based on the anaesthesiologists' heavy workload. The total number of anaesthesiologists approached could be an overestimation because some anaesthesiologists may a member of multiple societies, which could be an explanation of the low response rate. Furthermore, except for ESPA members, we do not know how many anaesthesiologists actually read the e-mailed invitation and did not respond, or how many anaesthesiologists missed the e-mail because it was relegated to the "spam" folder. Furthermore, since physicians receive at least one survey daily, it is not likely that they participate in every survey.[41]

The majority of respondents in this survey use dexmedetomidine in paediatric anaesthesia, despite its off-label

status and the lack of protocols. Dexmedetomidine provides sedation with minimal respiratory depression and quick onset mechanism. Furthermore, it quickly wears off, augments analgesia and is associated with only mild adverse drug reactions that rarely require treatment. Intercontinental sharing of experience and information would be desirable. Due to the off-label use and lack of evidence on dexmedetomidine in children, a consensus amongst experts on the use of this promising drug is decisive for the future use. Peer-reviewed protocols, dosage recommendations and teaching opportunities would be helpful in sharing the promising properties and safety of dexmedetomidine in paediatric care.

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References

1. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. *Rev Bras Anestesiol.* 2012;62(1):118-133.

2. Sulton C, McCracken C, Simon HK, et al. Pediatric Procedural Sedation Using Dexmedetomidine: A Report From the Pediatric Sedation Research Consortium. *Hosp Pediatr.* 2016;6(9):536-544.

3. Bellon M, Le Bot A, Michelet D, et al. Efficacy of Intraoperative Dexmedetomidine Compared with Placebo for Postoperative Pain Management: A Meta-Analysis of Published Studies. *Pain Ther.* 2016;5(1):63-80.

4. Szmuk P, Andropoulos D, McGowan F, et al. An open label pilot study of a dexmedetomidine-remifentanil-caudal anesthetic for infant lower abdominal/lower extremity surgery: The T REX pilot study. *Paediatr Anaesth.* 2019;29(1):59-67.

5. Gupta A, Dalvi NP, Tendolkar BA. Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: A prospective randomized double blind trial. *J Anaesthesiol Clin Pharmacol.*2017;33(2):236-240.

6. Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee LH. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. *Anesth Analg.* 2007;105(2):374-380.

7. Weatherall M, Aantaa R, Conti G, et al. A multinational, drug utilization study to investigate the use of dexmedetomidine (Dexdor®) in clinical practice in the EU. *Br J Clin Pharmacol.*2017;83(9):2066-2076.

8. FDA. PRECEDEX Safety and Drug Utilisation Review. *FDA.* 2016.

9. van Hoorn CE, Hoeks SE, Essink H, Tibboel D, de Graaff JC. A systematic review and narrative synthesis on the histological and neurobehavioral long-term effects of dexmedetomidine. *Paediatr Anaesth.* 2019;29(2):125-136.

10. Sanders RD, Sun P, Patel S, Li M, Maze M, Ma D. Dexmedetomidine provides cortical neuroprotection: impact on anaesthetic-induced neuroapoptosis in the rat developing brain. *Acta Anaesthesiol Scand.* 2010;54(6):710-716.

11. ClinicalTrial.gov. A phase I study of dexmedetomidine bolus and infusion in corrective infant cardiac surgery: safety and pharmacokinetics. https://clinicaltrials.gov/ct2/show/NCT01915277. Published 2019. Accessed September 16, 2019.

12. Damian MA, Hammer GB, Elkomy MH, Frymoyer A, Drover DR, Su F. Pharmacokinetics of Dexmedetomidine in Infants and Children After Orthotopic Liver Transplantation. *Anesth Analg.*2020;130(1):209-216.

13. Uusalo P, Guillaume S, Siren S, et al. Pharmacokinetics and Sedative Effects of Intranasal Dexmedetomidine in Ambulatory Pediatric Patients.*Anesth Analg.* 2019.

14. van Dijkman SC, De Cock P, Smets K, et al. Dose rationale and pharmacokinetics of dexmedetomidine in mechanically ventilated new-borns: impact of design optimisation. *European journal of clinical pharmacology.* 2019;75(10):1393-1404.

15. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine.*Clin Pharmacokinet.* 2017;56(8):893-913.

16. Zimmerman KO, Wu H, Laughon M, et al. Dexmedetomidine Pharmacokinetics and a New Dosing Paradigm in Infants Supported With Cardiopulmonary Bypass. *Anesth Analg.* 2019;129(6):1519-1528.

17. Tait AR, Voepel-Lewis T. Survey research: it's just a few questions, right? *Paediatr Anaesth.* 2015;25(7):656-662.

18. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. *Br J Anaesth.* 2015;115(2):171-182.

19. FDA. FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women.*Communications DS.* 2016.

20. Hansen TG. Use of anesthetics in young children Consensus statement of the European Society of Anaesthesiology (ESA), the European Society for Paediatric Anaesthesiology (ESPA), the European Association of Cardiothoracic Anaesthesiology (EACTA), and the European Safe Tots Anaesthesia Research Initiative (EuroSTAR). *Paediatr Anaesth.*2017;27(6):558-559.

21. Al-Zaben KR, Qudaisat IY, Al-Ghanem SM, et al. Intraoperative administration of dexmedetomidine reduces the analgesic requirements for children undergoing hypospadius surgery. *Eur J Anaesthesiol.*2010;27(3):247-252.

22. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. *Can J Anaesth.* 2006;53(7):646-652.

23. Olutoye OA, Glover CD, Diefenderfer JW, et al. The effect of intraoperative dexmedetomidine on postoperative analgesia and sedation in pediatric patients undergoing tonsillectomy and adenoidectomy.*Anesth Analg.* 2010;111(2):490-495.

24. Song J, Ji Q, Sun Q, Gao T, Liu K, Li L. The Opioid-sparing Effect of Intraoperative Dexmedetomidine Infusion After Craniotomy. *J Neurosurg Anesthesiol.* 2016;28(1):14-20.

25. Vilo S, Rautiainen P, Kaisti K, et al. Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. *Br J Anaesth.* 2008;100(5):697-700.

26. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clinical pharmacokinetics.* 2017;56(8):893-913.

27. Jin S, Liang DD, Chen C, Zhang M, Wang J. Dexmedetomidine prevent postoperative nausea and vomiting on patients during general anesthesia: A PRISMA-compliant meta analysis of randomized controlled trials.*Medicine.* 2017;96(1):e5770-e5770.

28. Yu YM, Shin WG, Lee JY, et al. Patterns of Adverse Drug Reactions in Different Age Groups: Analysis of Spontaneous Reports by Community Pharmacists. *PLoS One.* 2015;10(7):e0132916.

29. Smith MC, Williamson J, Yaster M, Boyd GJC, Heitmiller ES. Off-Label Use of Medications in Children Undergoing Sedation and Anesthesia.*Anesthesia & Analgesia.* 2012;115(5):1148-1154.

30. Tobin JR. Use of pharmaceuticals 'off-label' in the neonate. *Best Pract Res Clin Anaesthesiol.* 2010;24(3):451-460.

31. Pratico AD, Longo L, Mansueto S, et al. Off-Label Use of Drugs and Adverse Drug Reactions in Pediatric Units: A Prospective, Multicenter Study. *Curr Drug Saf.* 2018;13(3):200-207.

32. Gore R, Chugh PK, Tripathi CD, Lhamo Y, Gautam S. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. *Curr Clin Pharmacol.* 2017;12(1):18-25.

33. Goh AN, Bagshaw O, Courtman S. A follow-up survey of total intravenous anesthesia usage in children in the U.K. and Ireland. *Paediatr Anaesth.* 2019;29(2):180-185.

34. O'Brien MA, Rogers S, Jamtvedt G, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev.* 2007(4):Cd000409.

35. Flodgren G, Parmelli E, Doumit G, et al. Local opinion leaders: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev.* 2011(8):Cd000125.

36. Martin F, Bannard-Smith J, Blackburn T. Dexmedetomidine: a valuable sedative currently not widely available in the UK. *Br J Anaesth.*2016;117(2):263-264.

37. Agency EM. Assessment Report: Dexdor. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002268/WC500115632.pdf. Published 2011. Accessed 27 March, 2020.

38. Plambech MZ, Afshari A. Dexmedetomidine in the pediatric population: a review. *Minerva Anestesiol.* 2015;81(3):320-332.

39. Flint RB, van Beek F, Andriessen P, et al. Large differences in neonatal drug use between NICUs are common practice: time for consensus? *Br J Clin Pharmacol.* 2018;84(6):1313-1323.

40. Yang F, Liu Y, Yu Q, et al. Analysis of 17 948 pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine. *Paediatr Anaesth.* 2019;29(1):85-91.

41. Brasel K, Haider A, Haukoos J. Practical Guide to Survey Research. *JAMA Surgery.* 2020.

Table 1. Baseline characteristics of all respondents

	Total
Member	
Response rate	791
Do you use dexmedetomidine in paediatric anaesthesiology?	**Do you use dexmedetomidine in paedi**
Yes	552
No	206
Missing	33
Total	791
What type of hospital do you work at?	**What type of hospital do you work at**
Tertiary	558
Paediatric	116
Secondary	87
Primary	21
Missing	9
Total	791
What percentage of your work includes paediatric anaesthesiology?	**What percentage of your work include**
10%	44
25%	74
50%	88
75%	169

	Total
100%	402
Missing	14
Total	791
What type of anaesthesiologist are you?	**What type of anaesthesiologist are yo**
Paediatric	693
Ped training	29
General	43
Resident	7
Missing	19
Total	791

Table 2. Dexmedetomidine dosages reported by respondents (median with interquartile ranges, minimum and maximum dose).

Setting	Bolus min ug*kg^{-1}	Bolus min ug*kg^{-1}	Bolus max ug*kg^{-1}	Bolus max ug*kg^{-1}	IV min mg*kg/h^{-1}	IV min mg*kg/h^{-1}	IV max mg*kg/h^{-1}	IV ma mg*kg
Premedication	2.00	2.00	2.00	2.00	1.50	1.50	2.50	2.50
(nasal)	[1.00-2.00]	[1.00-2.00]	[2.00-3.00]	[2.00-3.00]	[0.50-4.00]	[0.50-4.00]	[1.00-4.25]	[1.00-4.25]
Min - max	0.00	5.00	0.20	5.00	0.25	5.00	0.50	5.00
Procedural sedation	1.00 [0.50-2.00]	1.00 [0.50-2.00]	1.10 [1.00-2.38]	1.10 [1.00-2.38]	0.50 [0.30-1.00]	0.50 [0.30-1.00]	[0.70-1.75]	[0.70-1.
Min - max	0.00	8.00	0.20	8.00	0.00	2.50	0.20	6.00
Intensive care sedation	1.00 [0.50-1.00]	1.00 [0.50-1.00]	[0.50-1.05]	[0.50-1.05]	0.50 [0.30-0.70]	0.50 [0.30-0.70]	[0.70-1.50]	[0.70-1.
Min - max	0.50	8.00	0.50	8.00	0.00	5.00	0.10	7.00
Anaesthesia	0.50 [0.50-1.00]	0.50 [0.50-1.00]	1.00 [0.50-1.00]	1.00 [0.50-1.00]	0.50 [0.30-0.70]	0.50 [0.30-0.70]	1.00 [0.50-1.00]	1.00 [0.50-1.00]
Min - max	0.00	2.00	0.00	4.00	0.00	5.00	0.03	4.00
Postoperative analgesia	0.50 [0.40-0.50]	0.50 [0.40-0.50]	0.50 [0.50-1.00]	0.50 [0.50-1.00]	0.40 [0.20-0.50]	0.40 [0.20-0.50]	0.50 [0.43-1.00]	0.50 [0.43-1.00]
Min - max	0.00	2.00	0.20	3.00	0.00	1.00	0.10	2.00
Other	0.50 [0.30-1.00]	0.50 [0.30-1.00]	0.85 [0.50-1.00]	0.85 [0.50-1.00]	0.90 [0.50-1.75]	0.90 [0.50-1.75]	[0.78-2.00]	[0.78-2.
Min - max	0.10	2.00	0.20	5.00	0.10	2.00	0.60	3.00

Median [IQR] and minimum and maximum (min – max) dosage administered.

Lowest and highest reported doses for bolus and continuous infusion of dexmedetomidine.

All settings, except for premedication, was mainly administered intravenously.

Table 3. Responses of respondents who use dexmedetomidine

	Total
	552
Is there a protocol available in your centre?	**Is there a protocol available**
Yes. a protocol is available	402
No. no protocol is available	102
Missing	48
Total	552
In what age categories do you use dexmedetomidine?*	**In what age categories do yo**
- 0-3 months old	363
- 3 months to 1 year	404
- 1 to 4 years	330
- 4 to 6 years	291
- 6 to 12 years	388
- older than 12 years	256
For what purposes do you use dexmedetomidine?*	**For what purposes do you u**
For premedication	255
For procedural sedation	375
For IC sedation	251
For anaesthesia	93
For postoperative analgesia	178
What adverse drug reactions have you experienced?[a]	**What adverse drug reaction**
Hypotension	78
Hypertension	20
Bradycardia	129
Hypoxia	55
Apnoea	9
Nausea	99
Emergence delirium	16
None	275
Are you familiar with any contraindications for the use of dexmedetomidine?	**Are you familiar with any co**
Yes. I am familiar with contraindications	170
No. I am not familiar with contraindications	350
Missing	32
Total	552
How would you rate your experience with dexmedetomidine? Median [IQR]	**How would you rate your ex**

[a]multiple answers possible

Table 4. Responses of respondents who do not use dexmedetomidine

	Total 206
Are you trained in the use of dexmedetomidine?	**Are you trained in the use of dexmedetomidine?**
Yes	23
No	182

	Total 206
Missing	1
Total	206
Are you familiar with dexmedetomidine?	**Are you familiar with dexmedetomidine?**
Yes	89
No	90
Missing	3
Total	182
Are you willing to start using dexmedetomidine?[a]	**Are you willing to start using dexmedetomidine?[a]**
Yes. I am willing to start using	174
Yes: good alternative	38
Yes: benefits of the drug	82
Yes: literature information	4
Yes: if recommended	3
Yes: if more information is available	7
Yes: other	40
Total	174
No. I am not willing to start using	29
No: better alternative	7
No: not registrated in country	4
No: no protocols	0
No: no need	9
No: price	1
No: more experience needed	7
No: other	1
Total	29
For what purposes would you use dexmedetomidine?[a]	**For what purposes would you use dexmedetomidine**
For premedication	126
For procedural sedation	133
For IC sedation	58
For anaesthesia	75
For postoperative analgesia	48
Missing	1
Other	8

[a]multiple answers possible

Figure legends

Figure 1. Distribution and response diagram of the survey

Figure 2. Reasons why respondents started using dexmedetomidine

Multiple answers possible

Figure 3. Reasons why respondents do not use dexmedetomidine

Multiple answers possible