ABSTRACT

Introduction It has been reported that post-hospitalisation behaviour change (PHBC) occurs in over 50% of children undergoing a general anaesthetic and manifests as behaviours such as sleep and eating disorders, defiance of authority, nightmares, enuresis and temper tantrums. The effect is usually short-lived (2–4 weeks); however, in 5–10% of children, these behaviours can last up to 12 months. The risk factors for developing PHBC include underlying anxiety in the child or parent, a previous bad hospital experience, emergence delirium and preschool age. A recent meta-analysis of alpha-2 agonists (including dexmedetomidine) found that they effectively reduce the incidence of emergence delirium but none of the studies looked at longer term outcomes, such as PHBC.

Methods and analysis Two-year-old to seven-year-old children requiring general anaesthesia for common day-case procedures will be randomly assigned to one of three groups: a dexmedetomidine premedication group, an intraoperative dexmedetomidine group and a control group. Baseline anxiety levels of the parent will be recorded and the anxiety of the child during induction of anaesthesia will also be recorded using validated tools. The primary outcome will be negative behaviours after hospitalisation and these will be measured using validated tools. The primary outcome will be negative behaviours after hospitalisation and these will be measured using the Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery and the Strengths and Difficulties Questionnaire. These questionnaires will be administered by a blinded researcher at days 3, 14 and 28 post surgery.

Ethics and dissemination Ethics approval has been granted by the Children’s Health Queensland human research ethics committee (HREC/15/QRCH/248) and the University of Queensland human research ethics office (#2016001715). Any amendments to this protocol will be submitted to the ethics committees for approval.

Trial registration number ANZCTR:1261600006459; Pre-results.

INTRODUCTION

Post-hospitalisation behaviour change (PHBC) after surgery and anaesthesia can be a significant problem for children and parents. The reason children exhibit such negative behaviour changes may be related to the psychological impact of the experience and there may also be a biological component directly related to brain changes from the anaesthesia, the stress response to the procedure and pain associated with the procedure. PHBC manifests as a variety of problematic behaviours, including separation anxiety, sleep disturbances, eating disturbances and aggression.1 For some children, these problems persist for months after the operation.2 Dexmedetomidine administered in the perioperative period may be effective at reducing the incidence of PHBC, but currently there is no evidence to support its use and a randomised, controlled trial is needed to assess its effectiveness.3

Incidence

The true incidence of PHBC is unknown with wide ranges reported in the literature. Fortier and Kain studied 260 children from the USA undergoing adenotonsillectomy and found 80.4% had PHBC on day 1 post procedure and nearly a third had PHBC on day 14.1 In an older study, Kain et al found that 54% of
children had PHBC on day 14 with 20% continuing to have problems 6 months after surgery and 7% having persistent problems at 1 year post procedure. Another study by Kain et al. found the incidence of PHBC at 14 days to be approximately 30%. A study from the UK by Power et al. looked at 131 children undergoing elective surgery and found that 73% had PHBC on day 2 after discharge and 32% still exhibited problem behaviour after 4 weeks. In Finland, Kotiniemi et al. studied 551 children undergoing surgery and anaesthesia and found the incidence of PHBC to be 46% on the day of surgery and 9% after 4 weeks. An Australian study by Stargatt et al. found significant PHBC in 24% of nearly 1000 children on day 3 after a variety of surgical procedures. This incidence dropped to 16% by day 30.

How PHBC is measured?

There are a number of reasons to explain the wide range of incidences reported in the literature. There may be cultural and institutional differences between the study populations and some of the studies only looked at one type of procedure or a subset of the general paediatric population. There are also methodological differences in the selection, allocation and analysis of subjects. One major difference is how the Post Hospitalisation Behaviour Questionnaire (PHBQ) is used. The PHBQ is the most commonly used measurement tool for studies examining PHBC after surgery and anaesthesia. It has been used hundreds of times in the psychology and anaesthesia literature. It was developed in the 1960s and consists of 27 items of behaviour that are rated by parents. Vernon et al. developed the tool based on six studies of children’s behaviour after hospitalisation in the 1950s. Symptoms that were mentioned in two or more of the studies were included in the questionnaire. The items on the questionnaire can be grouped into six subscales: general anxiety, separation anxiety, sleep anxiety, eating disturbance, aggression towards authority and withdrawal/apathy. The original study by Vernon et al. performed the PHBQ on 387 children aged 6 months to 16 years. The internal consistency (Cronbach’s alpha) varied from 0.45 to 0.73 for the subscales and was 0.82 for the overall score. The validity was tested by comparing PHBQ scores with ratings of 20 children by a child psychologist. Another study by Karling et al. found the PHBQ to have better internal consistency than the original study with Cronbach’s alpha of 0.81–0.87 for the subscales and 0.92 overall. It also confirmed the face validity of the factors by consensus of a panel of child psychologists. Another study by Karling and Hagglof examined the correlation between the PHBQ and the Child Behaviour Checklist (CBCL). The CBCL assesses 100 items for children aged 2–4 and 113 items for older children. It divides problem behaviours into internalising behaviours (withdrawn, somatic complaints and anxious–depressed) and externalising behaviours (delinquent behaviour, destructive behaviour and aggressive behaviour). It found moderate correlation for children aged 2–7, but no correlation for children aged 7 or above. The authors suggest that perhaps the PHBQ reflects more subtle changes in behaviour after a stressful event, whereas the CBCL may represent more general behavioural problems. However, it does suggest that the PHBQ is more suited to a younger age group and that perhaps school age children are not as affected by surgery and anaesthesia or that the PHBQ may not reflect the behaviours of school age children.

One of the major problems with the PHBQ is that no cut-off score was described in the original study. The definition of PHBC varies between studies with some defining PHBC as any deterioration in behaviour, while others set a minimum number of negative behaviours that need to be observed for PHBC to be present. For example, the study by Stargatt et al. that found an incidence of PHBC of 24% on day 3 post procedure defined PHBC as seven or more negative behaviour changes. The mean number of negative behaviour changes on day 3 was 4.4. Another difference is that some studies use the relative version of the PHBQ and others use the absolute version. The relative version asks parents to rate each of the 27 behaviour items relative to the child’s behaviour preoperatively on a five-point Likert scale (much less than before, less than before, the same, more than before and much more than before). The absolute version uses a four-point scale (never to always) and is administered preoperatively to get a baseline score and then again at various time points postoperatively. It has been suggested that the relative version, as originally described by Vernon et al., is more sensitive but may be more subjective.

Jenkins et al. have recently developed a revised PHBQ that reduces the number of items from 27 to 11. The Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery (PHBQ-AS) was developed by examining the California Irvine School of Medicine database of children who had been assessed using the PHBQ in 17 studies over 15 years (n=1064, mean age=5.88). A factor analysis was performed which could not replicate the original six subscale structure of the PHBQ. A principal components analysis then identified potential items on the questionnaire that were redundant and a panel of experts decided which items should be retained based on content validity. The reliability was found to be high for both the PHBQ and the PHBQ-AS (Cronbach’s alpha 0.82 and 0.8, respectively) and concurrent validity was assessed by correlating both questionnaires with the Functional Disability Inventory (Pearson’s r=0.48 and 0.49, respectively). The authors suggest that the revised, shortened questionnaire may be more relevant for day-case procedures as well as being more efficient.
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and more valid. However, the authors also state that until further validation of the revised questionnaire occurs, it may not be suitable for use in postoperative behavioural research. We will use this version of the PHBQ in this study and concurrently administer the Strengths and Difficulties Questionnaire (SDQ), a well-validated behavioural screening questionnaire. When compared with the CBCL, the SDQ was found to be significantly better at detecting inattention and hyperactivity and at least as good as detecting internalising and externalising problems. It was also preferred by parents.

Risk factors for PHBC

Many studies have tried to identify risk factors associated with PHBC after surgery and anaesthesia. Younger age, anxiety of the child, anxiety of the parent, previous bad hospital experience and longer hospital stay have all been reported to be associated with PHBC. Postoperative pain was found to be not significantly correlated with PHBC in studies by Stargatt and Fortier, but pain on the day of operation was found to be predictive of PHBC up to 4 weeks postoperatively by Kotiniemi et al (OR 4.44, 95% CI 3.4 to 5.48, P=0.0005). According to most studies, there is no association between the type of procedure and PHBC; however, one study by Kain found that PHBC was less frequent with minor Ears, Nose and Throat (ENT) procedures compared with other ENT and general surgical procedures. There does not appear to be any association between the type of induction and the development of PHBC. This is supported by the results of multiple studies. The use of premedication has conflicting results. Studies by Kain et al and McCluskey et al show significantly less PHBC with the use of premedication; however, other studies show no difference or even increased PHBC when midazolam premedication is used. Other risk factors that have been reported to increase the incidence of PHBC include two or more older siblings, a higher level of parental education and having a discussion with the anaesthetist preoperatively.

METHODS AND ANALYSIS

Aims of the study

The aim of this study is to measure the incidence of negative behaviour change in three groups of children:

1. Children who receive dexmedetomidine as premedication prior to day-case surgery and a placebo infusion intraoperatively.
2. Children who receive a placebo premedication and then an intraoperative infusion of dexmedetomidine during day-case surgery.
3. Children who receive a placebo premedication and a placebo intraoperative infusion during day-case surgery.

Objectives

1. To determine if dexmedetomidine reduces the incidence of negative behaviour change after day-case surgery and anaesthesia.
2. To determine if dexmedetomidine needs to be given as a premedication or whether the same effect can be gained from an intraoperative dose.

Hypothesis

Primary hypothesis

H0: The incidence of negative behaviour change will be the same in the dexmedetomidine groups as the control group.

HA: The incidence of negative behaviour change will be less in the dexmedetomidine groups compared with the control group.

Secondary hypothesis

H0: The incidence of negative behaviour change will be the same in the premedication and intraoperative groups.

HA: The incidence of negative behaviour change will be different in the premedication and intraoperative groups.

Study design

The study will be a randomised, controlled, superiority trial with three groups: a dexmedetomidine premedication group, a dexmedetomidine intraoperative group and a control group, randomised 1:1:1.

Study setting/location

The study will be conducted in the operating theatres and anaesthesia department of the Lady Cilento Children’s Hospital, Brisbane.

Study population

The study sample will be drawn from children presenting for elective surgery at the Lady Cilento Children’s Hospital. Children booked for elective day-case procedures will be screened for eligibility and sent information packs with their appointment letters.

Eligibility criteria

Inclusion criteria

► Age 2–7 years inclusive.
► American Society of Anaesthesiologist (ASA) 1 or 2.
► Booked for day-case surgical and radiological procedures.

Exclusion criteria

► ASA 3 or above.
► Emergency surgery.
► Allergy to dexmedetomidine.
► Currently taking antihypertensive medication.
► Existing behavioural problems/attention deficit hyperactivity disorder (ADHD)—defined as being under the care of a paediatrician for behavioural problems or currently taking medication for behavioural issues/ADHD.
Children assessed as needing a premedication by the attending anaesthetist on the day of surgery.

Surgery less than 10 min duration.

**Study outcomes**

**Primary outcome**
The primary outcome will be the presence of PHBC, defined as score of 3 or more on the PHBQ-AS.

**Secondary outcomes**
Secondary outcomes will be: adverse effects, emergence delirium, pain in recovery, analgesic requirements in recovery, time in recovery, pain at home, parental days off work, general practitioner (GP) visits related to post-hospitalisation behaviour change (PHBC) and parental satisfaction.

**Other data**
Data will be collected on:
1. Child characteristics: age, gender, previous surgeries, number of siblings, birth order, temperament and anxiety at induction.
2. Parent characteristics: age, occupation, level of education, salary, marital status, ethnicity, preparation received and anxiety (baseline and at induction).
3. Procedure characteristics: type of surgery, type of induction, intraoperative analgesia and length of surgery.

**Study procedures**

**Recruitment of participants**
Parents of preschool aged children (age 2–7 years inclusive) who are booked for elective surgery will be sent a brochure about the study. Subsequently a researcher will contact the family to determine if they are interested in participating. If so, a researcher will obtain consent on admission to the Surgical Admissions Lounge on the day of the procedure.

**Randomisation**
Randomisation will occur at the time of consent of enrolled and consenting participants. We have used unrestricted randomisation, in a 1:1:1 ratio, generated using an on-line randomisation system (Griffith University, Brisbane, Australia) The researcher, parents and children will be blinded to group allocation. Similarly, those assessing the outcomes of the study will be blinded to group allocation. Allocation concealment will be via the on-line randomisation system and only nurses involved in the drug preparation will be aware of the group allocation.

**Study procedure**
The bookings for elective procedures will be screened for eligible subjects. Eligible children and their families will be sent information about the study prior to the day of surgery. A researcher will contact the family to determine if they are interested in participating and if so they will meet a researcher on the day of admission in the Surgical Admissions Lounge of the Lady Cilento Children’s Hospital.

Once written consent is obtained, the child will be randomly allocated to one of three groups using an on-line randomisation programme. The allocation will be done by an intensive care nurse who is not involved with the study. This means that the researchers, children, parents and anaesthetists will be blinded to group allocation.

At this time, the researcher will collect demographic and baseline data from the family. This includes:

- Child’s age, gender, number of siblings, birth order and number of previous surgeries.
- Parent’s age, marital status, level of education, salary, ethnicity and preparation received.
- Type of surgery.
- The child’s temperament will be measured using the Emotionality, Activity, Sociability Temperament Survey (EAS).
- The parent’s baseline anxiety will be measured using the State-Trait Anxiety Inventory (STAI).
- A baseline score on the Strengths and Difficulties Questionnaire will be obtained.
- A score on the Modified Yale Preoperative Anxiety Scale (m-YPAS) will be obtained by a researcher prior to the intervention while the child is in the holding bay.

Forty minutes prior to the procedure, the children will receive a nasal spray (acceptable range 15–80 min). Children in the dexmedetomidine premedication group will receive 2 μg/kg of dexmedetomidine (dexametomidine HCl, Precedex; Hospira, Lake Forest, Illinois, USA) via a mucosal atomisation device (LMA MAD—Teleflex, SanDiego, California, USA). The dexmedetomidine will be made up using 100 μg/mL solution. Children in the other two groups will receive a nasal spray of identical volume of saline prepared by an intensive care nurse to look identical to the study drug.

Children will then be accompanied by a parent to the operating theatre where an anaesthetist blinded to group allocation will induce general anaesthesia by an inhalational or intravenous method at their discretion. A researcher will record the child’s anxiety at induction using the m-YPAS.

After induction, the anaesthetist will administer an intravenous solution over 10 min. Children in the intraoperative analgesia group will receive 1 μg/kg of dexmedetomidine made up in a solution of 0.9% saline to a concentration of 1 μg/mL. Children in the other two groups will receive the same volume of 0.9% saline made up by an intensive care nurse to look identical to the study drug.

After the procedure, the child will be taken to recovery where a researcher will record any adverse effects, intraoperative analgesia used by surgeon and anaesthetist, initial pain score in recovery, analgesic requirements, emergence delirium and time to discharge from recovery to the ward. Any unexpected overnight admission will be noted.

On day 3 after the procedure, the parents of the child will be contacted by a researcher by phone and
the presence of any negative behaviour changes will be assessed using the PHBQ-AS and the SDQ. At this time, they will also record the child’s pain score and parental satisfaction with the anaesthetic. Parental time off work and GP visits will also be recorded. The same measure will be repeated on days 14 and 28.

Data will be collected and managed using REDCap electronic data capture tools hosted at Griffith University, Queensland, Australia. The database will be password protected and only accessible to the research team. After data collection is complete, data source verification will be done on 20% of records for quality assurance.

Sample size and statistical power
Based on published data of trials that have used the same diagnostic criteria as this study, there is a 64% rate of negative behaviour change on day 3 post-op. As a conservative estimate, the underlying incidence has been set at 50% and a clinically significant reduction has been defined as a 50% reduction to a 25% rate. The sample size was calculated by the following method:

\[ n_i = \frac{2 \left( \frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\text{ES}} \right)^2}{\beta} \]

where \( n_i \) is the sample size required in each group, \( \alpha \) is the selected level of significance and \( Z_{1-\alpha/2} \) is the value from the standard normal distribution holding \( 1-\alpha/2 \) below it, and \( 1-\beta \) is the selected power and \( Z_{1-\beta} \) is the value from the standard normal distribution holding \( 1-\beta \) below it.

If \( \alpha=0.05 \), then \( 1-\alpha/2=0.975 \), \( Z=1.960 \).

If \( \beta=0.1 \), then \( 1-\beta=0.9 \), \( Z=1.282 \).

ES is the effect size, defined as follows:

\[ ES = \frac{|p_1-p_2|}{\sqrt{p(1-p)}} \]

where \( |p_1-p_2| \) is the absolute value of the difference in proportions between two of the groups expected under the alternative hypothesis and \( p \) is the overall proportion, based on pooling the data from the two comparison groups.

If there is a 50% rate of negative behaviour change on day 3 post-op and a clinically significant reduction would be a 50% reduction to a 25% rate, then:

\[ p_1=0.5, \ p_2=0.25, \ p=0.375 \]

\[ ES=0.5-0.25/\sqrt{0.375 \times (1-0.375)} = 0.25/0.48 = 0.52 \]

\[ n=2(1.96+1.282)/0.52 \]

\[ =78 \]

Therefore, we need 78 patients per group to detect a 50% reduction in NBC on day 3 post-op, assuming power of 90% and an alpha error of 0.05. Loss to follow-up is estimated to be between 5% and 20%, which would result in an overall sample size of 234–294 if recruitment continues until there are 78 complete day 3 follow-ups in each group.

Statistical methods
Baseline characteristics will be compared using Student’s t-test for continuous variables and \( \chi^2 \) analysis for categorical variables.

The \( \chi^2 \) test will be used to compare changes in proportion of PHBC over time.

Stepwise multiple binary logistic regression will be used to analyse relationships between baseline characteristics and PHBC. Only independent predictor variables will be retained in the final model.

Analysis of covariance will be used where groups are compared in relation to baseline measures. This will reduce the effect of regression to the mean from the comparison.

Linear mixed-effects modelling will be used for repeated measures over time (ie, the PHBQ and SDQ on days 3, 14 and 28).

Measurement tools used
EAS—The Emotionality, Activity, Sociability Temperament Survey is a parent report scale that assesses child temperament using 20 items in four behavioural categories. Total score ranges from 20 to 100 with higher scores in each category reflecting increased levels of those temperament traits.

STAI—The State Trait Anxiety Inventory is a self-report instrument that measures anxiety at baseline (trait) and at a specific time point (state). It consists of 20 questions at each time point. Scores range from 20 to 80 for each section with higher score indicating higher anxiety. It has been reported that during a stressful event the mean STAI scores are 43.01 for men and 43.69 for women.

m-YPAS—The Modified Yale Preoperative Anxiety Scale consists of 27 items rated by an observer to measure a child’s preoperative anxiety. It has five domains: activity, expressivity, arousal, vocalisation and use of parents. It gives a score from 0 to 100 with scores >30 indicating high anxiety.

PHBQ-AS—The Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery is an 11-item parental report measure used to assess negative behaviour change after hospitalisation. Each item will have a ‘Not Applicable’ option to avoid problems with missing data. A summed score will be obtained by allocating a score of 1–5 for each item with any ‘Not Applicable’ responses scoring 3 indicating no behaviour change. A score above 3 indicates the presence of negative behaviour change, a score of 3 indicates no change in behaviour and a score less than 3 indicates an improvement in behaviour. The results will be dichotomised into the presence or absence of PHBC and also calculated as a continuous variable.

SDQ—The Strengths and Difficulties Questionnaire is a validated behaviour screening tool for children aged 2–16. It has 25 items on five scales (some positive and some negative). We will use the follow-up versions for 2-year-olds to 4-year-olds and 4-year-olds to
10-year-olds. These versions are designed for use after an intervention.24

PAED and CAP-D—The Paediatric Emergence Delirium and the Cornell Assessment of Paediatric Delirium scales will be used to detect emergence delirium/agitation in recovery. The PAED Scale is currently used in our institution and the CAP-D includes three additional items that are designed to detect hypoactive and mixed delirium.25

NRS—A Numeric Rating Scale is a segmented numeric version of the Visual Analogue Scale in which the parent selects a whole number (0–10 integers) that best reflects the intensity of their child’s pain with 0 being no pain and 10 the worst pain imaginable. This will be used for parents when assessing their child’s pain at home.

FLACC—The Face, Legs, Activity, Cry, Consolability Scale is a validated pain measurement tool for children aged 2 months to 7 years. It gives a score of 0–10 with higher scores indicating higher levels of pain. It will be used to assess pain in recovery.26

DISCUSSION

Dexmedetomidine is a highly selective alpha-2 agonist that produces drowsiness, anxiolysis and analgesia. It causes minimal respiratory depression and it has a shorter duration of action than clonidine. It has poor bioavailability when given orally (around 15%) but is effective and well tolerated when administered intranasally or buccally. A recent meta-analysis by Pickard et al3 showed that an intraoperative dose of dexmedetomidine reduced the incidence of emergence delirium in children (OR 0.22, 95% CI 0.14 to 0.33, P<0.001). There were no differences in time spent in recovery or time to discharge. There was also a reduced need for rescue analgesia and this finding has been replicated by another meta-analysis by Schnabel et al27 that found decreased postoperative pain in children following an intraoperative dose of dexmedetomidine. There is also growing evidence that dexmedetomidine is neuroprotective in both animal and human models. A meta-analysis by Man et al28 found adults who had an intraoperative dose of dexmedetomidine had better neurocognitive outcomes compared with placebo and midazolam. Another meta-analysis by Pasin et al29 examined critically ill patients in an intensive care setting and found dexmedetomidine reduced the incidence of agitation, confusion and delirium compared with control. Other interesting findings from recent meta-analyses have shown decreased levels of interleukin (IL)-6, IL-8, tumour necrosis factor-alpha, serum catecholamine levels and serum cortisol levels in patients who received perioperative dexmedetomidine.20 21

In summary, dexmedetomidine reduces anxiety and pain in the perioperative period which may have an influence in reducing negative behaviour change postoperatively. It also has neuroprotective effects, anti-inflammatory effects and an ability to modulate the stress response. All of these effects may also contribute to longer term benefits.

PHBC is a significant problem related to childhood surgery and anaesthesia with an incidence of over 50% reported in various studies. It may also persist for up to a year in a small percentage of children.2 Risk factors include preschool age, child anxiety, parental anxiety, length of hospital stay and previous bad hospital experience.3 5–7 It is a significant problem as it may have long-term effects on the child’s compliance with future medical therapy and it has been suggested that distress surrounding medical procedures in children leads to an increase in pain and anxiety surrounding medical events as adults.1 Given that around 6 million children undergo general anaesthesia every year in the USA, including 1.5 million preschool age children, this has major public health implications.32 In addition to the effects on the child, it has been reported that PHBC in children postoperatively results in parents taking additional time off work and additional visits to GPs.3

Dexmedetomidine has been shown to reduce emergence delirium but longer term outcomes such as PHBC have not been assessed. Kain et al33 found that there is a link between emergence delirium and negative behaviour changes at home. They looked at 1279 children who had been involved in post-hospitalisation behaviour studies and found an OR of 1.43 (95% CI 1.09 to 1.88) for children who experienced emergence delirium to develop PHBC. This study will compare the incidence of PHBC in children who are given dexmedetomidine either preoperatively or intraoperatively with a placebo. The study will answer the question of whether dexmedetomidine reduces PHBC in preschool age children. In addition, it will indicate whether the dose of dexmedetomidine needs to be given as a premedication to be effective. Most of the interventional studies on PHBC have assumed that reducing preoperative anxiety will reduce PHBC postoperatively; however, dexmedetomidine may have neuroprotective, anti-inflammatory and analgesic effects that make it equally effective if it is given intraoperatively.

Data Safety Monitoring Board

A Data Safety Monitoring Board has been established with a clinical trials pharmacist from our institution plus two independent clinicians with expertise in this field. Any serious adverse events will be reported to both the DSMB and the ethics committee.

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REFERENCES

1. Fortier MA, Kain ZN. Treating perioperative anxiety and pain in children: a tailored and innovative approach. Paediatr Anaesth 2015;25:27–35.
2. Kain ZN, Mayes LC, O’Connor TZ, et al. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med 1996;150:1238–45.
3. Pickard A, Davies P, Birnie K, et al. Systematic review and meta-analysis of the effect of intraoperative α2-adrenergic agonists on postoperative behaviour in children. Br J Anaesth 2014;112:982–90.
4. Kain ZN, Mayes LC, Wang SM, et al. Postoperative behavioral outcomes in children: effects of sedative premedication. Anesthesiology 1999:90:758–65.
5. Power NM, Howard RF, Wade AM, et al. Pain and behaviour changes in children following surgery. Arch Dis Child 2012;97:879–84.
6. Kotiniemi LH, Ryhänen PT, Molianen IK. Behavioural changes in children following day-case surgery: a 4-week follow-up of 551 children. Anaesthesia 1997;52:970–6.
7. Stargatt R, Davidson AJ, Huang GH, et al. A cohort study of the incidence and risk factors for negative behavior changes in children after general anesthesia. Paediatr Anaesth 2006;16:06060603719027–59.
8. Vernon DT, Schulman JL, Foley JM. Changes in children’s behavior after hospitalization. Some dimensions of response and their correlates. Am J Dis Child 1966;111:981–93.
9. Karling M, Stenlund H, Hägglöf B. Behavioural changes after anaesthesia: validity and liability of the Post Hospitalization Behavior Questionnaire in a Swedish paediatric population. Acta Paediatr 2006;95:340–6.
10. Karling M, Hägglöf B. Child behaviour after anaesthesia: association of socioeconomic factors and child behaviour checklist to the Post-Hospital Behaviour Questionnaire. Acta Paediatr 2007;96:418–23.
11. Jenkins BN, Fortier MA, Kaplan SH, et al. Development of a short version of the modified Yale Preoperative Anxiety Scale. Anesth Analg 2014;119:643–50.
12. Goodman R, Scott S. Comparing the strengths and difficulties questionnaire and the child behavior checklist: is small beautiful? J Abnorm Child Psychol 1999;27:17–24.
13. Fortier MA, Del Rosario AM, Rosenbaum A, et al. Beyond pain: predictors of postoperative maladaptive behavior change in children. Paediatr Anaesth 2010;20:445–53.
14. Kain ZN, Wang SM, Mayes LC, et al. Distress during the induction of anesthesia and postoperative behavioral outcomes. Anesth Analg 1999;88:1042–7.
15. Foesel T, Reisch HJ. Postoperative behavioural changes in children: comparison between halothane and sevoflurane. Paediatr Anaesth 2001;11:719–23.
16. Kotiniemi LH, Ryhänen PT. Behavioural changes and children’s memories after intravenous, inhalation and rectal induction of anaesthesia. Paediatr Anaesth 1996;6:201–7.
17. Aguilera IM, Patel D, Meakin GH, et al. Perioperative anxiety and postoperative behavioural disturbances in children undergoing intravenous or inhalation induction of anaesthesia. Paediatr Anaesth 2003;13:501–7.
18. Keaney A, Diviney D, Harte S, et al. Postoperative behavioral changes following anesthesia with sevoflurane. Pediatr Anesthesiology 2004;14:866–70.
19. McCluskey A, Meakin GH. Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. Anaesthesia 1994;49:782–5.
20. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. Paediatr Anaesth 1998;8:117–21.
21. Buss AH, Plomin R. Temperament: early developing personality traits. Hillsdale, CA: Lawrence Erlbaum Associates, 1984.
22. Spielberger D. State-trait anxiety inventory (STAI). Palo Alto, CA: Consulting Psychology Press, 1983.
23. Kain ZN, Mayes LC, Cicchetti DV, et al. The Yale Preoperative Anxiety Scale: how does it compare with a “gold standard”? Anesth Analg 1997;85:783–8.
24. Goodman R, The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997;38:581–6.
25. Bajwa SA, Costi D, Cyyna AM. A comparison of emergence delirium scales following general anesthesia in children. Paediatr Anaesth 2010;20:704–11.
26. Merkel SI, Voepel-Lewis T, Shayevez JH, et al. The FLACC: a behavioral scale for scoring postoperative pain in young children. Paediatr Nurs 1997;23:293–7.
27. Schnabel A, Reichl SU, Poeping DM, et al. Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: a meta-analysis of randomized controlled trials. Paediatr Anaesth 2013;23:170–9.
28. Han Y, Guo Z, Cao J, et al. Efficacy of perioperative dexmedetomidine in postoperative neurocognitive function: a meta-analysis. Clin Exp Pharmacol Physiol 2015;42:837–42.
29. Pasin L, Landoni G, Nardelli P, et al. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2014;28:1459–66.
30. Li B, Li Y, Tian S, et al. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: a meta-analysis. Sci Rep 2015;5:12342.
31. Wang XY, Cao JB, Lv BS, et al. Effect of perioperative dexmedetomidine on the endocrine modulators of stress response: a meta-analysis. Clin Exp Pharmacol Physiol 2015;42:828–36.
32. Sun L. Early childhood general anaesthesia exposure and neurocognitive development. Br J Anaesth 2010;105(Suppl 1):61–83.
33. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg 2004;99:1648–54.