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RESEARCH ARTICLE

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Preoperative anxiety level is not associated with postoperative negative behavioral changes in premedicated children

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Abstract

Background: Anesthesia preinduction anxiety in children can according to some studies lead to long-term anxiety and negative behavioral changes (NBC), while other studies have not found this effect. This secondary analysis from a recent premedication trial comparing clonidine and midazolam aimed to test the relation between preoperative anxiety assessed with modified Yale Preoperative Anxiety Scale (mYPAS) and postoperative NBCs assessed with Post Hospital Behavior Questionnaire (PHBQ), regardless of premedication type.

Methods: This is a planned secondary analysis from a published premedication comparison trial in an outpatient surgery cohort, children aged 2–7 years. Participant and preoperative factors, particularly preoperative anxiety as mYPAS scores, were assessed for association with development of postoperative NBCs.

Results: Fifty-four of the 115 participants had high preinduction anxiety (mYPAS >30), and 19 of 115 developed >3 postoperative NBCs 1 week after surgery. There was no association between preinduction anxiety level as mYPAS scores and the development of postoperative NBCs at 1 week after surgery (10 of 19 had both, $p = .62$) nor after 4- or 26-weeks post-surgery. Only lower age was associated with development of NBCs postoperatively.

Conclusions: Based on the findings from this cohort, high preinduction anxiety does not appear to be associated with NBCs postoperatively in children premedicated with clonidine or midazolam.

KEYWORDS
children, postoperative negative behavioral changes, postoperative recovery, preoperative anxiety

Editorial Comment

The authors previously published a prospective randomised controlled trial comparing oral midazolam and clonidine premedication in young children. This secondary analysis reports no effect of increased pre-operative anxiety on long term postoperative negative behavioural changes up to 26 weeks. This is re-assuring, however, it remains to be seen if this is an effect of either premedication as an un-premedicated group was not included in the original study.

1 | INTRODUCTION

High levels of preoperative or anesthesia preinduction anxiety in children are undesirable. Preinduction anxiety may influence many aspects of the perioperative period, including the efficacy of anesthetic drugs, anesthetic emergence, the child's general hospital experience, and more. Specifically, some studies have shown that anxiety/distress at anesthesia induction can lead to increased postoperative pain, long-term anxiety problems and new or regressive negative behavioral changes (NBCs).[1–6] This evidence provides motivation for actively attempting to reduce preanesthetic anxiety levels in children. However, other studies have not demonstrated an association between preanesthetic anxiety levels and new postoperative NBC.[7–9] These results bring into question whether levels of preanesthesia anxiety in children are associated with or could predict postoperative negative outcomes. In this secondary analysis of results from a recently published premedication trial in children,[10] we aimed to assess the relationship between preinduction anxiety level in premedicated children and development of postoperative NBC, regardless of premedication type. The null hypothesis is that there is no relationship between preanesthetic anxiety scores and postoperative NBC.

2 | METHODS

This study received ethical approval (Umeå 2012-417-31M and 2013-354-32M, Anders Iacobaeus chairman) and informed consent was given by the parents of the participants. Pre-enrollment trial registration was performed with the Swedish Medical Products Agency (Lars Hedlund, April 12, 2013, EudraCT number: 2012-005215-42, https://eudract.ema.europa.eu). The study was conducted according to the Declaration of Helsinki. This report comprises a planned secondary analysis of the database previously used with the primary goal to assess two different premedications for postoperative NBCs.[10]

The trial design details have been published elsewhere.[10] A brief overview is presented here. Inclusion criteria were children 2–7 years with ASA physical status I-II undergoing outpatient ear, nose, or throat surgery at a single center, Skellefteå, Sweden. Exclusion criteria included unplanned surgery, not accepting premedication, or parents not understanding the Swedish language.

On the day of surgery, after informed consent was obtained, participants received one of two alternative premedications (randomly allocated), either clonidine 4 μg/kg orally or midazolam 0.5 mg/kg orally, allowing appropriate times from administration to expected maximum effect (60 and 30 min, respectively) before entering the operating room. The clinicians caring for the patient, the parents, the pre-anesthesia anxiety assessors, and postoperative assessors were blinded to which premedication was given. In the operating room, with parents accompanying their children, the participants were managed by one standard anesthesia protocol for intravenous access and intravenous anesthetic induction, with inhalational anesthetic maintenance. They all had been prepared with a local anesthetic cream (EMLA, Aspen Nordic) on arm/hand in two places 60 min before. One intravenous (iv) cannula was inserted for intravenous induction with fentanyl 1 μg/kg and propofol 3–4 mg/kg. If venous access was difficult or very stressful for the child, mask induction with sevoflurane-nitrous-oxide was performed. Propofol 1 mg/kg iv bolus was given at the start of anesthesia emergence, to try to prevent agitation

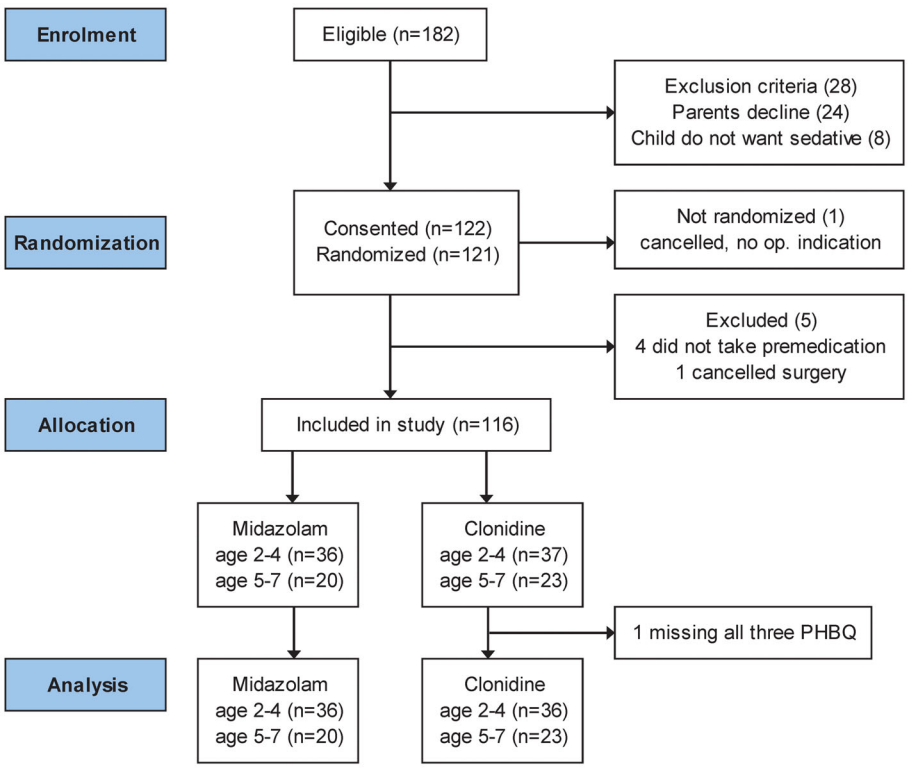

FIGURE 1 CONSORT flowchart from original study.[10]

TABLE 1 Demographic and other factors by preoperative anxiety.

	mYPAS <30 ($n = 61$)	mYPAS >30 ($n = 54$)	*p*
Premedication			
Clonidine	17 (29%)	42 (71%)	<.001
Midazolam	44 (79%)	12 (21%)	<.001
Age			
Months (mean, SD)	61.4 ± 18.4	51.9 ± 15.5	.004
Sex			
Male	37 (53%)	33 (47%)	
Female	24 (53%)	21 (47%)	1.00
Maternal education			
University	32 (52%)	29 (48%)	
Lower	29 (54%)	25 (46%)	.99
Paternal education			
University	27 (55%)	22 (45%)	
Lower	34 (52%)	32 (48%)	.58
Child living with			
2 adults	57 (53%)	51 (47%)	
Only mother	4 (67%)	2 (33%)	.80
Siblings (mean, SD)	1.5 ± 0.9	1.4 ± 0.9	.78
City size			
Urban	37 (61%)	24 (39%)	
Rural	22 (42%)	30 (58%)	.06
Previous hospitalizations			
Yes	25/61 (41%)	19/54 (35%)	.57
Previous anesthesia			
Yes	18/61 (30%)	9/54 (17%)	.13
Previous negative experience			
Yes	9/61 (15%)	8/54 (15%)	1.00
Previous family trauma			
Yes	4/61 (7%)	1/52 (2%)	.37
Tonsil surgery	15/61 (25%)	12/54 (22%)	.83

Note: Data are presented as either mean with variation or *n* (%). Mean difference performed with independent *t*-test. Comparisons of proportions done with chi-squared test.
Abbreviations: CI, confidence interval; mYPAS, modified Yale Preoperative Anxiety Scale, Urban = >10,000 inhabitants, Rural = <10,000 inhabitants; SD, standard deviation.

TABLE 2 PHBQ outcome and mYPAS status at the three assessment points.

Number of NCBs	mYPAS <30, *n*	mYPAS >30, *n*	Total, *n*	*p*
PHBQ at 1 week				
0–3 new NBCs	52	44	96	
>3 new NBCs	9	10	19	.62
Total	61	54	115	
PHBQ at 4 weeks				
0–3 new NBCs	56	49	105	
>3 new NBCs	5	5	10	1.00
Total, *n*	61	54	115	
PHBQ at 26 weeks				
0–3 new NBCs	59	49	108	
>3 new NBCs	2	5	7	.25
Total, *n*	61	54	115	

Abbreviations: mYPAS, modified Yale Preoperative Anxiety Scale; PHBQ, Post Hospital Behavior Questionnaire.
p-Values from Fisher's exact test 2 sided.

TABLE 3 Frequencies number of NBCs at 1 week by preoperative mYPAS score.

mYPAS score intervals	NBC = 0, *n*	NBC = 1, *n*	NBC = 2, *n*	NBC = 3, *n*	NBC = 4, *n*	NBC = 5, *n*	NBC = 6, *n*	NBC = 7, *n*	NBC >7, *n*
23.3–28.3	32	11	7	2	3	4	1	1	
31.6–38.3	11	3	6			1	1		
41.6–48.3	2	1	1	1	1			1	
51.6–58.3	7					1	1		1
61.6–68.3	4		1						
70.0–76.6	3								
81.6–86.6		1		1	1				
90.0–100	1		1		1	1			

Abbreviations: mYPAS, modified Yale Preoperative Anxiety Scale; NBC, negative behavioral change; PHBQ, Post Hospital Behavior Questionnaire.

TABLE 4 Frequencies number of NBCs at 4 weeks by preoperative mYPAS score.

mYPAS score intervals	NBC = 0, *n*	NBC = 1, *n*	NBC = 2, *n*	NBC = 3, *n*	NBC = 4, *n*	NBC = 5, *n*	NBC = 6, *n*	NBC = 7, *n*	NBC >7, *n*
23.3–28.3	46	6	3	1	3			1	1
31.6–38.3	15	3	1	1	2				
41.6–48.3	6		1						
51.6–58.3	6	2	1						1
61.6–68.3	3	1		1					
70.0–76.6	1	1		1					
81.6–86.6	1			1					1
90.0–100			2	1		1			

Abbreviations: mYPAS, modified Yale Preoperative Anxiety Scale; NBC, negative behavioral change; PHBQ, Post Hospital Behavior Questionnaire.

TABLE 5 Frequencies number of NBCs at 26 weeks by preoperative mYPAS score.

mYPAS score intervals	NBC = 0, *n*	NBC = 1, *n*	NBC = 2, *n*	NBC = 3, *n*	NBC = 4, *n*	NBC = 5, *n*	NBC = 6, *n*	NBC = 7, *n*	NBC >7, *n*
23.3–28.3	40	9	3	7	1			1	
31.6–38.3	18			3	1				
41.6–48.3	6			1					
51.6–58.3	5	1	2		1				1
61.6–68.3	2	1	1						1
70.0–76.6	2				1				
81.6–86.6	2			1					
90.0–100	3		1						

Abbreviations: mYPAS, modified Yale Preoperative Anxiety Scale; NBC, negative behavioral change; PHBQ, Post Hospital Behavior Questionnaire.

upon emergence.[11] Postoperative analgesia was also defined by the same protocol, with paracetamol and possibility for ketorolac or morphine administration based on pain scoring as described in the protocol, with paracetamol and ibuprofen allowed after leaving the post-anesthesia unit.

2.1 | Assessment instrument

The modified Yale Preoperative Anxiety Scale (mYPAS)[12] was used, an observational assessment instrument containing 22 items in five categories: activity, emotional expressivity, state of arousal, vocalization, and use of parents. The highest behavioral score in each of the five categories was used as the ordinal result for that category. Categories had either 4 or 6 items, and these were weighted to generate a total score from 0 to 100 for defining level of observed anxiety.

The participants were assessed with the mYPAS instrument by a study-based observer, from the time of entering the operating theater with their parents until the anesthesia induction was completed. No mYPAS assessment was performed before premedication. The highest observed mYPAS value per participant was recorded. A cutoff for positive mYPAS was set at above 30 points[12] and an actual score of 30 is not possible with the mYPAS instrument.

TABLE 6 Secondary outcomes by mYPAS.

	mYPAS < 30 Total, $n = 61$ (yes/no)	mYPAS > 30 Total, $n = 54$ (yes/no)	p
Nausea 1	9/52	10/44	.62
Clonidine	1/16	7/35	
Midazolam	8/36	3/9	
Vomiting 1	9/52	16/38	.07
Clonidine	1/16	10/32	
Midazolam	8/36	6/6	
FPS-R 1 > 3 (total, $n = 52$)	5/28	4/17	.72
Clonidine	0/11	2/14	
Midazolam	5/17	2/3	
FLACC 1 > 3 (total, $n = 68$)	10/21	6/31	.16
Clonidine	2/5	3/25	
Midazolam	8/16	3/6	
Rescue morphine	16/45	9/45	.26
Clonidine	4/13	4/38	
Midazolam	12/32	5/7	
Nausea 2	15/46	6/47	.09
Clonidine	4/13	3/38	
Midazolam	11/33	3/9	
Vomiting 2	12/49	7/46	.45
Clonidine	3/14	4/37	
Midazolam	9/35	3/9	
FPS-R 2 > 3 (total, $n = 56$)	12/23	4/17	.36
Clonidine	6/6	3/15	
Midazolam	6/17	1/2	
FLACC 2 > 3 (total, $n = 70$)	4/27	5/34	1.00
Clonidine	1/6	3/26	
Midazolam	3/21	2/8	
Adverse event	17/44	17/37	.69
Clonidine	4/13	14/28	
Midazolam	13/31	3/9	

Note: Adverse event = such as excessive tiredness, prolonged nausea/vomiting, infections. Fisher's exact test for p value.

Abbreviations: FLACC 1, pain assessed with Face, Legs, Activity, Cry, Consolability at the recovery room; FLACC 2, postoperative pain assessed with Face, Legs, Activity, Cry, Consolability the first 24 h at home; FPS-R 1, pain assessed with Faces Pain Scale revised at the recovery room; FPS-R 2, postoperative pain assessed with Faces Pain Scale Revised the first 24 h at home; Nausea 1, postoperative nausea at the recovery room; Nausea 2, postoperative nausea the first 24 h at home; Rescue morphine, morphine given postoperatively in the recovery room; Vomiting 1, Postoperative vomiting at the recovery room; Vomiting 2, postoperative vomiting the first 24 h at home.

2.2 | Outcomes

The main outcome was new postoperative NBC identified using the Post Hospital Behavior Questionnaire (PHBQ).[13,14] The details concerning this outcome have been presented earlier.[10] In brief, PHBQ involves 25 individual questions, divided into the following categories: general anxiety, withdrawal, eating disturbances, separation anxiety, regression, aggression, and sleep anxiety. The reporting for each question was on a scale from 1 to 5, where 3 indicated no change in behavior and 4–5 was indicative of a new NBC. A positive outcome was defined as more than 3 new NBCs reported by parents. PHBQ events were reported by parents at 1 week, 4 weeks, and 26 weeks after the operation. The primary assessment point for PHBQ was new NBCs at 1 week after the operation. Secondary outcomes include NBCs at 4 and 26 weeks, pain scoring, and occurrence of nausea and vomiting in the recovery room or on the first

day at home, rescue morphine directly postoperatively, and adverse events including new symptoms for prolonged nausea/vomiting within the first week. Instruments used for pain scoring were Face Legs Activity Cry Consolability (FLACC)[15,16] and Faces Pain Scale-Revised (FPS-R).[17,18] The FLACC instrument is for observed behavior, designed for children who cannot estimate in words their level of pain. A FLACC sum of 0 stands for no pain and 10 for maximum pain. FPS-R uses the child's own selection from six different faces showing no pain (score 0) to maximum pain (score 10).

2.3 | Analysis

Complete case analysis was used for both the exposure condition and the PHBQ outcome. Where specific PHBQ questions were left blank by parents, this was included in the analysis as no change. To assess proportions for exposures and outcome, Chi squared test or the Fisher's exact test was used (IBM SPSS Statistics for Windows, 2019 Version 26.0, Armonk, NY). In the secondary analyses, multivariable logistic regression was used. Analysis of PHBQ results at 4 and 26 weeks, as well as for postoperative nausea/vomiting, pain, morphine, and adverse events, was purely explorative and descriptive. No adjustment for multiple comparisons was made. Additionally, premedication type was included in secondary regression analysis as a factor. To guide significance testing, a *p*-value level <.05 was used.

No specific sample size calculation was performed for this planned secondary post hoc analysis of the original premedication trial results.[10]

3 | RESULTS

Of the 182 children screened during the trial period 2014–2016, 120 completed the trial with 115 as complete cases for the primary data collection (Figure 1[10]). Positive results in the assessment of mYPAS, children with anxiety (mYPAS score > 30) were observed in 54 of the 115 participants. There was a significant risk of demonstrating signs of anxiety (mYPAS score > 30) at a younger age and/or if the participant had received clonidine premedication instead of midazolam. No other background factor was associated with degree of preoperative anxiety (Table 1). In the whole cohort, 19 of the 115 children developed significant NBCs (>3 new NBCs) 1 week after surgery, and younger age was also a risk factor for developing postoperative NBCs.

Regarding the main result, there was no association between clinically relevant preanesthetic anxiety signs as assessed by mYPAS and postop NBCs at 1 week assessed with PHBQ, where 10 of 19 had both (Fisher's exact test $p = .62$), as shown in Table 2. Frequencies with absolute numbers of NBC events can be seen for each mYPAS interval (Table 3), showing that some participants without anxiety (low mYPAS scores) developed postop-NBCs while others with high mYPAS scores did not demonstrate postoperative negative outcomes in terms of NBCs.

TABLE 7 Univariate analysis PHBQ at 1 week positive (>3 NBCs) by mYPAS.

	Odds ratio (OR)	95% CI for OR	*p*
mYPAS >30	0.76	0.28–2.04	.59
Premedication	1.79	0.65–4.93	.26
Age in months	0.96	0.93–1.00	.03

Abbreviations: mYPAS, modified Yale Preoperative Anxiety Scale; NBC, negative behavioral change; PHBQ, Post Hospital Behavior Questionnaire.

TABLE 8 Multivariable analysis PHBQ at 1 week by mYPAS as a continuous variable and age.

	Odds ratio (OR)	95% CI for OR	*p*
mYPAS total points	1.01	0.98–1.03	.52
Age in months	0.97	0.93–1.00	.06

Abbreviations: mYPAS, modified Yale Preoperative Anxiety Scale; PHBQ, Post Hospital Behavior Questionnaire.

Secondary results for mYPAS and PHBQ at 4 and 26 weeks are presented in Table 2, which show no association between positive mYPAS and positive NBCs at either of these assessment point. Frequencies for NBCs and mYPAS intervals at week 4 and week 26 are shown in Tables 4 and 5. Notably, many NBCs observed at 1 week after surgery did not persist at 4 and 26 weeks.

Further secondary analyses for mYPAS and other factors show that postoperative nausea/vomiting, pain, morphine, and adverse events were not associated with positive mYPAS (Table 6). Secondary results for factor associations to the main outcome, new NBCs, are partly shown in Table 7, where only age showed an association in univariate logistic regression. Based on this a further multivariate regression analysis for PHBQ positive at 1 week by age and mYPAS absolute score as a continuous variable showed no interaction (Table 8).

4 | DISCUSSION

The main finding in this secondary analysis of results from this trial[10] is that no association between scores indicative of high preanesthetic anxiety and postoperative new negative behaviors was observed in children premedicated with either clonidine or midazolam. This result does not mean that there is no influence from preanesthesia conditions on postoperative recovery, but rather that it could not be demonstrated in this cohort, and that a large effect is unlikely. This observation appears to be independent of type of premedication.

The preoperative anxiety outcome for the primary assessment was categorical, that is, mYPAS positive or negative based on a widely accepted cut-off of 30 points.[12,19–21] The range of mYPAS scores as a continuous factor and new NBCs 1 week after surgery also showed no association, so there was no indication that very high mYPAS scores had a different relationship to the outcome compared with barely positive mYPAS scores.

The only factor that was found to be associated with new NBCs was age in months. As noted in the primary study,[10] younger age was a significant factor in developing postoperative NBCs, where premedication type was a primary exposure. Younger age was also associated with higher mYPAS score, but again it was not necessarily the participants with high mYPAS score that developed NBCs postoperatively.

The context for this assessment was that premedication should have a consistent preanesthesia anxiety-limiting effect. The original trial was a superiority assessment comparing two premedication treatment for efficacy. Neither treatment was completely effective in preventing preoperative anxiety, and thereby there was a group of cases which had clear preoperative anxiety signs despite premedication. This anxiety condition was assessed and scored based on an established and validated set of physical signs. The premedication doses were chosen based on common practice and experience at the time, where it was recognized that a single dose is not always effective, but might need supplementation in everyday practice, though this not simply managed in this kind of trial. At the same time, no placebo (non-premedication) group was included, since premedication was the community standard of practice given the recognized high likelihood of preanesthesia anxiety when there is no premedication in this type of cohort.

Some reports have given support to the idea that the preanesthesia state of children will have an impact on postoperative child well-being as exemplified by behavior regression or new negative behaviors.[1–6] It is widely accepted that negative experiences for children in connection with healthcare or hospital contacts can have negative sequelae for children, at least in the short term.[22,23] A key issue in this current secondary analysis was to try to see if any of the many perioperative factors might have a meaningful impact on an individual child where negative experience could lead to later negative psychological developments which one might suspect to be a result of hospital experience. There are many possible factors other than preanesthesia anxiety level that might be relevant. Additionally, where there is potent premedication and anesthetic drug effects, it is challenging to understand which experiential imprints remain over time with children in this context. It is possible that a strong, and possibly negative, experience other than preanesthesia anxiety, such as pain, nausea, delirium, etc. can have left a strong negative impression with a child which could have a much larger effect than preanesthesia anxiety. The child's temperament and anxiety state before the hospital stay has also been suggested to have an impact on later NBCs.[24] Also factors like oxygen saturation, inflammation neurotoxicity and epigenetic changes are thought to be possible contributors to postoperative NBCs.[25,26] These are possible explanations for not finding an association between mYPAS and PHBQ scores with this cohort. It is still possible that there is some connection, albeit quite limited, between the two phenomena.

A strength in this study design is that the analysis could be performed in this prospectively controlled dataset independently for preanesthetic anxiety condition regardless of premedication type, where all other treatments were the same. Limitations in this study are that, for this secondary analysis, the sampling size was not designed to test this specific question. To detect small exposure effects, possibly a larger cohort would be needed. There were no mYPAS assessment prior to premedication which could be a limitation if there were expected differences in child anxiety state at arrival to the hospital. Our local experience prior to the study was that it was rare for children to express anxiety when entering the study center's Ear/Nose/Throat clinic and play area, though not having this assessment could mean that cases where there was steady pre-operative anxiety before any contact with healthcare workers would be missed as a factor. Another consideration for the mYPAS anxiety scoring system is that where some children could have more introverted anxiety, this would not be scored the same in the mYPAS instrument compared to children with extroverted expression of anxiety. This would not change the categorical outcome of positive or negative mYPAS since even being silent or not moving will generate a positive mYPAS result. Only playing and responding in a calm way will generate a negative mYPAS result.

Another limitation is the precision of the PHBQ instrument, which relies on parental interpretation and reporting, which is subjective. The one-week postoperative reporting interval is a compromise between enough distance from the operation and enough recency for optimal parental engagement. The PHBQ instrument itself is much discussed[26–28] concerning optimal scoring and analysis routines, and a validated single approach is not yet widely established. The PHBQ outcome definition used here is explained in some depth in the original trial publication.[10]

Premedication can be useful for calming an anxious child and to get a smooth anesthesia induction, but this may not affect the development of meaningful postoperative NBCs. Exactly what causes post-NBCs can be multifactorial and differ from child to child. This is one reason why it is important that the entire care during the hospital stay is supportive and of good quality from the child's perspective.

In conclusion, this secondary analysis of prospectively controlled treatments for a cohort of day surgery children premedicated with either clonidine or midazolam finds no relation between preanesthesia anxiety scores and postoperative new negative behaviors. A true relation between this exposure and these outcomes cannot be excluded based on these findings, but if a small exposure effect exists, it is possible that it could have been diluted by other types of exposures to participants in the perioperative period.

AUTHOR CONTRIBUTIONS

Caroline Zickerman contributed to the study design, data collection and analysis and manuscript writing. Camilla Brorsson contributed to the study design, data analysis and manuscript writing. Magnus Hultin contributed to the study design, data analysis and manuscript writing. Göran Johansson contributed to the study design, data collection and analysis and manuscript writing. Ola Winsö contributed to the study design, data analysis and manuscript writing. Michael Haney contributed to the study design, data collection and analysis and manuscript writing.

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CONFLICT OF INTEREST STATEMENT

No author has any competing interests to declare, other than Michael Haney is the current Editor in Chief of the Acta Anaesthesiologica Scandinavica journal.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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