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# Update on best current practice of non-pharmacological interventions reducing preoperative anxiety in children, a semi-systematic literature review

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**Abstract**: *Background:* Preoperative anxiety in children typically associates with emergence delirium, postoperative pain, analgesic need and new-onset maladaptive behavioral changes. Non-pharmacological interventions are able to reduce anxiety without need to expose children to drug therapy and it's possible side effects. The goal of our semi-systematic review is to provide an update on current best practice to reduce preoperative anxiety in children and improve cooperation during induction of general anesthesia with non-pharmacological interventions.
*Methods:* The Medline database was searched using Mesh terms ' anesthesia', anxiety' and 'children' for articles with publication date until November 2020. A total of 646 articles were identified and screened for inclusion based on their titles and abstracts by 2 independent reviewers. A total of 27 articles were included, 26 randomized controlled trials and 1 meta-analysis. Grading of evidence was conducted using a modified Bizzini score.
*Results:* Both distraction with cartoons and transporting the children in a toy car proved effective therapy. Same day mask exposure or creating a low sensory stimuli environment reduced anxiety. Parental presence during induction of general anesthesia showed no effect on reduction of anxiety level.
*Conclusions:* Distraction, same day mask exposure and low sensory stimuli are good interventions to reduce preoperative anxiety in children. Future research should include a larger study population and focus on children with comorbidities and behavioral problems which are known to increase their baseline anxiety.

**Key words:** preoperative anxiety; children; general anesthesia.

## Introduction

Surgery can be a fearful event, especially for young patients. The separation from parents, the unfamiliar faces and the unknown environment can cause anxiety. This preoperative anxiety is recognized as feelings of nervousness, worry and tension before a surgery. It manifests as crying, anger, verbal and behavioural unrest. Preoperative anxiety in children is associated with difficult induction of general anesthesia (GA), emergence delirium, increased postoperative pain, increased use of analgesia, new-onset maladaptive behavioral changes like sleep problems and parental separation anxiety (1-3). To reduce the stress and facilitate the induction of GA, children often receive sedative drugs. Premedication with benzodiazepines can lead to undesirable effects such as airway obstruction, delayed hospital discharge and behavioral changes (4, 5). Non-pharmacological interventions have been introduced to reduce preoperative anxiety in children. In 2015 the meta-analysis of Manyande et al. (6) already looked at different non-pharmacological interventions, concluding that acupuncture by parents, exposure to videogames, clowns or low sensory stimulation seemed promising in reducing preoperative anxiety. This review's goal is to give an update on the current best practice for both anesthesiologist, pediatricians, medical trainees, operating theatre nurses, psychotherapists and parents regarding non-pharmacological interventions in their attempt to reduce preoperative anxiety and improve cooperation during induction of GA. Furthermore, a guidance for future research will be provided.

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## Methods

### *Inclusion and exclusion criteria*

In this semi-systematic review, only randomized controlled trials and meta-analyses were included. The participants had to be children or adolescents aged under 18 years, who were scheduled to undergo any type of surgery under GA. Induction of GA could be intravenous or by inhalation anesthetics. Non-pharmacological interventions with the aim to reduce anxiety or improve compliance at the time of induction were included. Parental interventions or interventions with the aim to reduce parental anxiety were excluded. The non-pharmacological intervention could be compared with standard care, another non-pharmacological intervention or a pharmacological intervention.

### *Literature search*

A literature search was conducted in the Medline database in November 2020. The Mesh terms used were 'children', 'anxiety' and 'anesthesia'. Only articles in Dutch, French and English were withheld. The search was limited to randomized controlled trials and meta-analyses.

### *Grading of evidence*

To determine the quality of our selected randomized controlled trials, two researchers independently scored the articles based on the validated Bizzini scoring system (7). Most of the non-pharmacological interventions were impossible to blind. The Bizzini score is a score which ranges from 0 to 100, of which only 10% is based on blinding of the intervention. It also includes 4 main criteria (population, interventions, effect size, data presentation and analysis), which get a maximum score of 25 based on their 3 to 5 specific criteria (Appendix). The Bizzini score was easily applicable, however a modification on three points was made. First the points covering the follow up in the intervention category were changed, based on the findings of Kain et al. (3) regarding behavioral outcomes of preoperative anxiety. Second the subcategory blinded outcome assessment was altered. A score of 0/10 , 5/10 or 10/10 was given for no blinding, single blinded or double blinded trials respectively. The third change that was implemented, concerned the grading of the quality. Since some of the points were easily earned, scores below 50 were considered as very low evidence, scores from 50 to 74 as low evidence, from 75 to 89 as moderate evidence, 90 and higher as high quality evidence.

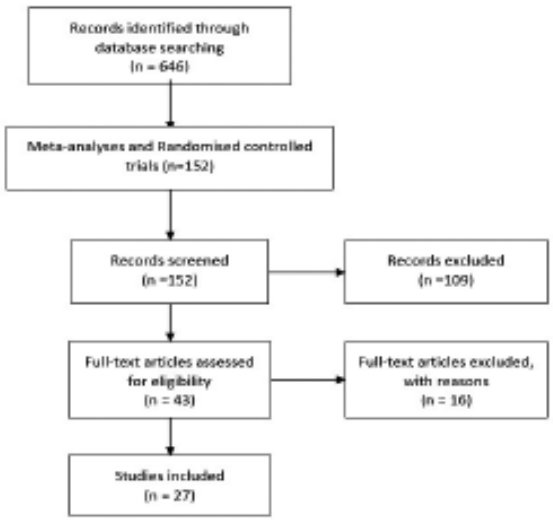


Fig. 1. — Prisma diagram of the literature search process.

### *Statistical analysis*

Descriptive statistics were applied, such as the mean, median, standard deviation, sample variance, skewness and kurtosis to describe the basic features of the two datasets. A Pearson correlation coefficient was determined to analyze the correlation between the scores of the two researchers and a Bland-Altman plot was used to identify any systematic difference between the scores or possible outliers. Our goals deemed necessary to accept the data, were a Pearson correlation coefficient higher than 0.7 and less than 15 points difference in score per article. However, if needed, outliers in our dataset presented by the Bland-Altman plot were corrected with the help of a third independent researcher. In that case the third researcher received the necessary information about the modified-Bizzini score and the corresponding article(s), blinded from the scores of the initial two researchers. After the third researcher's evaluation, the article(s) were discussed together and a consensus score was reached for these outlier(s). Except for the consensus score, the final score was an average of the two initial researcher's scores. All statistical analyses were performed with Excel version 16.45.

## Results

### *Including of the studies*

The Medline database was searched with the Mesh terms 'anesthesia', 'anxiety' and 'children'

resulting in 646 articles. Only randomized controlled trials and meta-analysis were withheld, this left us with 152 articles. One hundred and nine records were excluded for not meeting the inclusion criteria after a first screening based on the title and abstract of the article. Reasons for excluding were local anesthesia, parental anxiety as main outcome and isolated pharmacological interventions. The remaining 43 articles were assessed for eligibility by thorough reading. We included 27 articles in this review, consisting of one meta-analysis and 26 randomized controlled trials.

*Effect of the interventions*

1. Parental presence

Four of the studied articles investigated the effect of parental presence on preoperative anxiety (10-13). None of them showed a statistically significant reduction in anxiety levels in children due to parental presence during induction of GA. One review showed higher anxiety levels in the parental absent group at the time of separation from the parents, but the anxiety levels in both groups were equal during the actual induction of GA (13). Three of the studies used the modified Yale Preoperative Anxiety Scale (mYPAS). The study of Kain et al. (10) was the only one to use serum cortisol levels as an outcome parameter. In this review, the analysis of variance showed that the three following groups had lower levels of serum cortisol with parental presence: children older than 4 years, children whose parents had low levels of trait anxiety and children with low baseline level of activity based on temperament. Overall the results were not statistically significant. After analysis of variance in these three subgroups however,n there was a significant difference in anxiety. This suggests a possible advantage towards parental presence (10). Regarding the parents themselves, other studies of Kain et al. found that parents benefitted from being present during induction of GA of their child. This lead to more parental satisfaction (12) and less parental anxiety (11).

2. Education

Five articles investigated reduction of preoperative anxiety in children by educating them on what to expect during the perioperative period (8,14-17).

2.1. Educational programs

Three RCTs investigated the effect of preoperative educational programs on preoperative anxiety in children (14–16). Only Cuzzocrea et al. (16) could prove a significant reduction in anxiety and improved compliance during induction of GA after the educational program. However the evidence was qualified as low according to our modified Bizzini scores. Huntington et al. (14) showed no reduced preoperative anxiety in children with their intervention. This was a study performed in children undergoing dental extractions under GA, a possible explanation is that this group of patients is known for poor psychological well-being (34). Hee et al. (15) also studied the effect of preoperative education. They showed no reduction of anxiety during an intravenous anesthesia induction, however when there was a subsequent inhalation induction necessary there was reduced anxiety.

2.2. Informative virtual reality

Two RCTs looked at the effect of a virtual reality tour that gave information on what to expect during the perioperative period (8,17). They intended to inform the children, thereby reducing preoperative anxiety. Both studies were qualified as high level evidence randomized controlled trials based on our scores. They used the mYPAS and induction compliance checklist (ICC) to determine preoperative anxiety and compliance during induction of GA. Ryu et al. (17) showed a significant reduced anxiety and improved compliance during induction. Eijlers et al. (8) could not confirm a beneficial effect on children's anxiety. Remarkable in this study was the non-compliance in 21 children, of the 100 participants in the VR group discontinued the intervention by taking of the VR headset.

3. Distraction

Eight articles examined whether distraction of the child could reduce preoperative anxiety. (18–25) They each used different modalities of distraction.

3.1 Clowns

Three articles (18–20) focused on the use of clowns to comfort the children. All three studies confirmed the reduction in preoperative anxiety, two even proved that the anxiety levels were lower than in the premedication with midazolam group (18,19). At the time point of introducing the anesthesia mask, Golan et al. (18) showed no difference in anxiety and compliance between the clown group and control group. Remarkable is that even if the health professionals indicated that clowns were beneficial

for the children, they were opposed to continuing the program because of perceived interference with the procedures of the operating room (20). All three studies used the mYPAS to determine children's anxiety.

### 3.2 Transportation

Liu et al. (21) used toy cars to transport the children from the ward to the operating room in an attempt to distract them. They had lower levels of anxiety compared to the control group and the same levels of anxiety compared to the midazolam group. In this RCT six children were excluded, of which four patients refused to get on the gurney.

### 3.3 Smartphones

Cumino et al. (22) used smartphones to distract the children, resulting in lower anxiety levels in the intervention group. Videogames as a manner to reduce anxiety was investigated by Patel et al. (23) and proved to be efficient in reducing anxiety.

### 3.4 Cartoons

Two studies used cartoons to lower preoperative anxiety by distraction (24, 25) , one by using videoglasses to show the cartoons. Lee et al. (24) proved that children distracted by animated cartoons had lower levels of anxiety compared to the control group and the group who brought a toy. The study of Kerimoglu et al. (25) demonstrated that video glasses which showed animated cartoons led to equal low levels of anxiety as premedication with midazolam, but the quality of evidence was low. Almost 8% of the children did not comply by taking of the video glasses. Anxiety levels were measured with the mYPAS.

## 4. Environmental changes

### 4.1 Mask

Three articles investigated introduction to the anesthesia mask as a tool to reduce the preoperative anxiety in children. Gupta et al. (26) concluded that both flavored and non-flavored anesthesia masks led to the same levels of anxiety and equally good compliance during induction of GA based on the mYPAS and ICC. Two studies (27, 28) looked into preoperative exposure to the anesthesia mask. Both of them proved that preoperative exposure could lead to less anxiety and better compliance based on the mYPAS and ICC. Walker et al. (27) also looked at the timing of exposure. It seemed that the group who was exposed on the day of surgery had lower anxiety levels than the group who was exposed 3 times in the week before surgery. Aydin et al. also proved that induction time was shorter in the mask exposed group(28).

### 4.2 Sensory stimuli

The study of Kain et al. (29) evaluated the effect of decreased sensory stimuli by dimming the operating room lights, playing soft background music and letting only one person interact with the child. They confirmed that decreased sensory input during induction of anesthesia resulted in declined preoperative anxiety and increased compliance based on mYPAS en ICC. Two other studies used music therapy in their attempt to reduce anxiety (30,31). Neither of them could prove a benefit towards preoperative anxiety. Kain et al. (31) found a therapist dependent reduction in anxiety.

### 4.3 Intravenous or inhalation induction

One article compared intravenous and inhalation induction (32). They concluded that children were more anxious in the intravenous induction group. There was no difference in the incidence of behavioral disturbances in the first 2 weeks postoperatively.

### 4.4 Position

There was no difference in anxiety induced by the application of the anesthesia mask between the sitting and supine position group (33).

### 4.5 Acupressure

One article compared acupressure at the Extra-1 point and acupressure at a sham point. Acupressure is a non-invasive stimulation technique. Wang et al. (9) found that acupressure at the Extra-1 point led to lower levels of anxiety, but according to the modified Bizzini score the quality of evidence was low. There were no differences in depth of anesthesia measured by bispectral analysis of EEG levels or propofol need.

*Statistical analysis of grading of evidence*

The results from the descriptive statistics showed a mean of 80 and 84 points, a median of

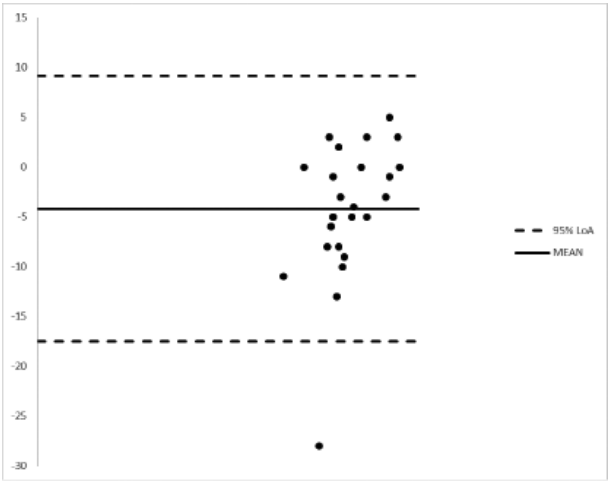


Fig. 2. — Bland-Altman plot.

78 and 85 points, a standard deviation of 9.6 and 6.5 points, a Kurtosis of 0.004 and -0.02, and a Skewness of -0.11 and -0.31 for the two researchers, respectively.

For 1 article, the article of Wang et al. (9) on acupressure, there was a 28 point difference between our two researchers (60 versus 88 points). The discrepancy was mostly based on the different scoring of the points for control group and the blinded outcome assessment (both with a maximum of 10 points). This was caused by different interpretation of the study design of the RCT. After discussion with the third reader, 67 points was agreed as the consensus score. The difference in score for all the remaining articles was less than 15 points. This was depicted in the Bland-Altman plot which showed a mean difference of 4.2 points, a lower limit of agreement of -17 points and a upper limit of agreement of 9 points (fig.2). Without correction of the outlier the Pearson correlation coefficient was 0.71 (above our threshold of 0.7). Five articles had a score of 90 or more and were considered as high quality evidence. Moderate quality of evidence was considered for 18 articles, three articles had low quality of evidence and zero articles had very low quality of evidence (table 1).

The Bland-Altman plot shows that for 25 out of 26 RCTs the difference in score fall within the limits of agreement (LoA) of 95%. MEAN = mean difference (-4.2 points), 95% LoA = 95% limits of agreement (upper LoA = 9 points, lower LoA = -17 points).

Note: there are 24 dots, because some articles did have the same difference in score between the researchers.

## Discussion

Numerous non-pharmacological interventions have the potential to exert beneficial effects on anxiety in children in the preoperative setting. In this semi-systematic review distraction of the children stood out as an effective option to lower children's level of preoperative anxiety and increase the compliance during induction of GA. However the quality of evidence varied from low to moderate (table 1). Although the results of the RCTs investigating distraction of children are positive, this has to be confirmed in bigger and higher quality trials. Transporting the child in a toy car to the operating theatre achieved the same low levels of anxiety as premedication. Recent literature shows the strength of virtual reality in the pre-operative setting. Notable was that in the RCTs with virtual reality and video glasses, there were surprisingly many dropouts due to equipment removal. The use of clowns also showed good results, however health professionals found it to be impractical and expensive. Unlike Manyande et al. (6) this approach is therefore not recommend as a standard of care. A recent insight is the favorable effect of same day mask exposure which, in contrast, is an easy and inexpensive intervention. After the meta-analysis of Manyande et al. (6) the beneficial effect of low sensory stimuli was reconfirmed with high quality of evidence. This included dimmed operating room lights, soft background music and only one person interacting with the child. Music therapy alone was not effective in reducing anxiety. From the three educational programs, only one showed reduction in anxiety. This was however a RCT with low quality of evidence. The informative virtual reality tour showed mixed results. None of the studies on parental presence could confirm its benefit. As Manyande et al. (6) already concluded in 2015 regarding reducing children's anxiety, parents should not be actively discouraged nor encouraged to be present during induction of anesthesia. Furthermore it's notable that the follow-up period for most RCTs was too short to see possible side effects of the interventions. Three RCT's combined the non-pharmacological interventions with oral premedication, which makes it more difficult to see the effect of the intervention itself. Almost all RCTs used patients of American Society of Anesthesiology classification I and II (table 1). They did not include children with more comorbidities who regularly need GA, or children with higher baseline level of anxiety (for example dental care patients). Induction of GA can be a bigger challenge

*Table 1*

Summary of all investigated RCTs.

| Author | year | Age | Num. of patients | dropouts | Induction | Intervention | Outcome | Score |
|---|---|---|---|---|---|---|---|---|
| Parental presence | | | | | | | | |
| Kain et al. (10) | 1996 | 1-6y ASA 1-2 | 84 | Not described | Inhalation | Parental presence vs parental absence (both groups with flavored mask) | No difference in anxiety | 87* |
| Kain et al. (11) | 2008 | 4.3y mean age ASA 1-2 | 61 | 3 (2 requested premedication) | Inhalation | 1 parent vs 2 parents | No difference in anxiety | 79* |
| Kain et al. (12) | 2000 | 2-8 y ASA 1-2 | 103 | 8 (5 refused to Swallow premedication) | Inhalation | Premedication vs premedication + parental presence | No difference in anxiety | 78* |
| Wright et al. (13) | 2010 | 3-6y ASA 1-2 | 61 | Not described | Inhalation | Parental presence vs no parental presence | No difference in anxiety | 76* |
| Education | | | | | | | | |
| Educational Programs | | | | | | | | |
| Huntington et al. (14) | 2018 | 5-7y ASA 1 | 117 | 10 (Rescheduled operations) | Inhalation | Preoperative Preparation program vs control vs placebo hand washing game | No difference in anxiety | 95[I] |
| Hee et al.(15) | 2012 | 6-15y | 100 | No dropouts | Intravenous (failed IV : inhalation ) | Education program vs control | No difference in anxiety | 95[I] |
| Cuzzocrea et al. (16) | 2013 | 3-12y | 50 | Not described | Inhalation | Psychological preparation vs distraction | Reduced anxiety and improved compliance during induction | 65[S] |
| Virtual Reality | | | | | | | | |
| Eijlers R. et al (8) | 2019 | 4-12y ASA 1-2 | 200 | 21 (took of VR) | Intravenous, if declined or unsuccessful: inhalation | Virtual reality vs control | No difference in anxiety | 93[I] |
| Ryu et al. (17) | 2017 | 4-10y ASA 1-2 | 70 | 1 (dizziness caused by VR) | Intravenous | Standard information vs VR tour guide | Reduced anxiety and improved compliance during induction | 85* |
| Distraction | | | | | | | | |
| Clowns | | | | | | | | |
| Golan et al. (18) | 2009 | 3-8y ASA 1-2 | 65 | Not described | Inhalation | Clowns vs midazolam vs control | Reduced anxiety preoperative, not during induction | 79* |
| Vagnoli et al. (19) | 2010 | 5-12y ASA 1-2 | 75 | Not described | Inhalation | Clown vs midazolam vs control | Reduced anxiety | 78* |
| Vagnoli et al. (20) | 2005 | 5-12y | 40 | Not described | Inhalation | Clown vs control | Reduced anxiety | 77* |
| Transport | | | | | | | | |
| Liu et al. (21) | 2018 | 2-5y ASA 2-3 (congenital hart disease) | 108 | 6 (4 patients refused to get on the gurney) | Intravenous | Transport toy car vs gurney vs gurney + midazolam | Reduced anxiety | 83* |
| Smartphones | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cumino et al. (22) | 2017 | 4-8y ASA 1-2 | 84 | Not described | Inhalation | Information leaflet parents vs smartphone distraction children vs information + smartphone vs control | Reduced anxiety in all intervent-ions groupscompared to control group | 85* |
| Patel et al. (23) | 2006 | 4-12y ASA 1-2 | 112 | Not described | Inhalation | Videogame vs midazolam vs control | Reduced anxiety | 79* |
| Cartoons | | | | | | | | |
| Lee et al. (24) | 2012 | 3-7y ASA 1-2 | 130 | 4 (children did not bring favorite toy) | Intravenous | Control vs toy vs animated cartoon | Reduced anxiety in cartoon group | 78* |
| Kerimoglu et al. (25) | 2013 | 4-9y ASA 1-2 | 96 | 6 (5 removed video glasses, 1 expelled midazolam) | Inhalation | Midazolam vs videoglasses vs midazolam + videoglasses | Reduced anxiety Videoglasses = midazolam | 70[§] |
| Environment/Equipment | | | | | | | | |
| Masks | | | | | | | | |
| Gupta et al. (26) | 2017 | 4-12y ASA 1-2 | 60 | No dropouts | Inhalation | Flavored masks vs masks without flavor | No difference in anxiety levels and compliance during induction | 93[ı] |
| Walker et al. (27) | 2018 | 4-7y | 110 | Not described | Inhalation | Mask exposure week before surgery vs mask exposure day of surgery vs control | Reduced anxiety and more compliance during induction (mask exposure day of surgery) | 81* |
| Aydin et al. (28) | 2007 | 3-7y ASA 1 - 2 | 50 | Not described | Inhalation | Preoperative mask Exposure vs control (both groups with midazolam) | Reduced anxiety and improved com-pliance during induction | 80* |
| Sensory stimuli | | | | | | | | |
| Kain et al. (29) | 2001 | 2-7 y ASA 1-2 | 70 | No dropouts | Inhalation | Low sensory stimulation group vs control | Reduced anxiety and improved compliance during induction | 92[ı] |
| Kühlmann et al. (30) | 2020 | 3-11y ASA 1-2 | 159 | 17 | Intravenous or inhalation | Music intervention pre-operative vs music intervention pre- and intraoperative vs control | No difference in anxiety | 87* |
| Kain et al. (31) | 2004 | 3-7y ASA 1-2 | 123 | Not described | Inhalation | Music therapy vs midazolam vs control | No difference in anxiety | 83* |
| Others | | | | | | | | |
| Aguilera et al. (32) | 2003 | 2-14y ASA 1-2 | 110 | 10 (3 children refused allocated method, 2 difficulty IV access) | Inhalation vs intravenous | Inhalation vs intravenous induction (both groups with midazolam) | More anxiety in intravenous induction group | 80* |
| Cohen et al. (33) | 2018 | 2-12y ASA 1-3 | 202 | 6 | Inhalation | Sitting vs supine Position (both groups with midazolam) | No difference in anxiety | 77* |
| Wang et al. (9) | 2008 | 8-17 y ASA 1-2 | 52 | Not described | Inhalation | Extra-1 acupressure vs sham point acupressure | Reduced anxiety | 67[§] |

To facilitate the discussion we subdivided the interventions into four main groups. Furthermore we illustrated the description of interventions assessed, their outcomes and the mean modified Bizzini scores of each randomized controlled trial. [ı]High quality of evidence. *Moderate quality of evidence. [§]Low quality of evidence

in this subcategory of patients. Most of the non-pharmacological interventions were impossible to blind. Therefore, the well-known Jadad scale was not used for grading of evidence, since the scale is based on blinding by 33%. Instead a modified Bizzini score was implemented, of which only 10% is based on blinding of the intervention. The Bizzini score was adopted but modified on 3 points as mentioned in the methods. This was necessary to guide our readers in their scoring and since the follow-up period for this types of interventions was shorter compared to the original Bizzini score.

### *Strengths and weaknesses*

A first weakness of this semi-quantitative review is the fact that most RCTs are small, mostly single center, studies. This indicates we can't always assume that the conclusion can be adopted for the general population. On the other hand a lot of the RCTs are well constructed and are of moderate to high quality of evidence according to the modified Bizzini score. Since research in this topic is scarce, these reviews are the best guides for our current practice, pending on further investigation. Second, Manyande et al. (6) already investigated non-pharmacological interventions with the intention of lowering preoperative anxiety in 2015 (included studies until 2013). However new research is constantly being published and this is apparent by the fact that one third of our included RCTs were performed after 2013. A strength of this semi-systematic review is that we determined the quality of evidence based on a modified Bizzini score. This was an effective way to improve our methodology and add value to our outcomes.

## Conclusion

### *Current best-evidence based approach*

Distraction by transportation in a toy car to the operating room, the use of smartphones, videogames and cartoon watching seemed the most efficient interventions to reduce preoperative anxiety in children undergoing GA. A recent insight is that same day mask exposure is an easy and efficient way to reduce anxiety. Another effective intervention is low sensory stimuli during induction of GA.

### *Future research*

Future research in this topic should contain larger patient groups and high quality trials to confirm our results and to find new interventions to reduce anxiety in children undergoing GA. Researchers should especially focus on the follow-up period and inclusion of children with more comorbidities and subgroups of patients known for their higher levels of anxiety. Future research should also look into different ways of distracting children as this proved to be promising. Newer technologies like video glasses and videogames could be investigated more in depth, focusing on a way to improve compliance with the intervention.

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**APPENDIX**

*Modified Bizzini score, used by the researcher to add grading of evidence to the randomized controlled trials.*

| | | |
|---|---|---|
| **POPULATION** | | /25 |
| Inclusion criteria | | /5 |
| Exclusion criteria | | /5 |
| Nul-hypothesis rejected 5/5<br>Nul-hypothesis not rejected, power? YES : 5/5, NO: 0/5 | | /5 |
| >25 patients: 5/5 11-15: 2/5<br>21-24 : 4/5 6-10: 1/5<br>16-20: 3/5 <5: 0/5 | | /5 |
| Homogeneity | | /5 |
| **INTERVENTION** | | /25 |
| Standardized and described | | /10 |
| Control group | | /10 |
| No co-interventions<br>Or co-interventions same for all groups | | /5 |
| **EFFECT SIZE** | | /25 |
| Relevant outcome | | /10 |
| Blinded outcome assessment<br>0 : No blinding<br>5: Single-blinded<br>10 : Double-blinded | | /10 |
| Follow up<br>2weeks: 3<br>6months: 4<br>> 1year: 5 | | /5 |
| **DATA ANALYSE** | | /25 |
| Randomization | | /5 |
| Description of dropouts, withdrawals | | **/5** |
| Intention to treat : withdrawals are included in analysis | | /5 |
| Proper statistical procedures described | | /10 |