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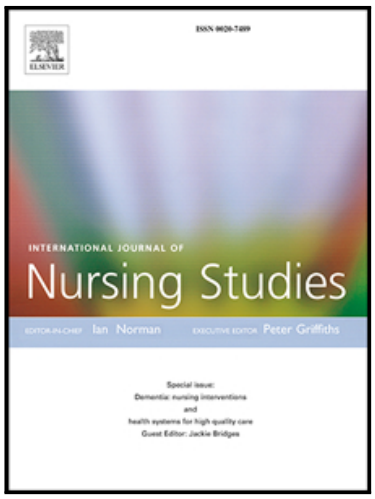

"Effectiveness of virtual reality in the management of paediatric anxiety during the peri-operative period: a systematic review and meta-analysis."

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Title: "Effectiveness of virtual reality in the management of paediatric anxiety during the peri-operative period: a systematic review and meta-analysis."

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Abstract

Background

Children undergoing surgery generally experience anxiety during the perioperative period, which could impact the surgical outcome, cause long-term psychological consequences and result in later healthcare avoidance. Preoperative anxiety in children is managed using both pharmacological and non-pharmacological therapies. The latter include distraction, a tour of the operating room and parental presence until the induction of anaesthesia. A novel and effective non-pharmacological therapies is the use of virtual reality to reduce anxiety and pain in children scheduled for medical procedures. However, the effectiveness of virtual reality in paediatric surgery has yet to be evaluated in a systematic review.

Objective

To evaluate the effectiveness of virtual reality in the management of anxiety in paediatric patients during the perioperative period.

Design

Both a systematic review and a meta-analysis of randomised controlled trials were performed according to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions Section 8.5 and in accordance with the Cochrane Effective Practice and Organisation of Care. The results are reported as prescribed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.

Data sources

A systematic search of randomised controlled trials was conducted using Medline, SCOPUS, Web of Science, Ovid MEDLINE and CINAHL.

Review methods

Two researchers screened potentially eligible articles and then assessed the quality of the reported studies using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions Section 8.5 and according to Cochrane Effective Practice and Organisation of Care.

The data were synthesised using the random-effects models to incorporate the estimated heterogeneity in the weighting. Heterogeneity was tested using the Q and I^2 statistics. The τ^2 statistic, an estimate of the amount of variation between the included studies, was also determined. Studies whose heterogeneity with respect to primary outcome measurements hindered pooling of the results for meta-analysis were summarised narratively.

Results

Seven studies were eligible for inclusion in this systematic review. An effect size for anxiety could be determined in six. The results support the effectiveness of virtual reality in reducing anxiety in paediatric patients undergoing elective surgery. The overall effect was supported by a confidence

interval < 0 (PL=−0.341, 95% confidence interval: −0.620 to −0.107) and by heterogenity indexes that were non significant (Q=9.49, p=0.091) or not important (I^2=38.64%).

Conclusions

Paediatric patients undergoing elective surgery may benefit from virtual reality as a distraction method that can reduce anxiety.

PROSPERO register, number: (blinded for Referee).

What is already known

- Virtual reality uses computer technology to create a simulated environment. In paediatric patients scheduled for surgery, it can be used to familiarise the child with the healthcare environment and as a distraction method that reduces anxiety.

What the paper adds

- Virtual reality offers an effective non-pharmacological approach to the management of anxiety in children during the preoperative period and therefore an alternative to analgesic drugs and their potential side effects.
- Further rigorous randomised controlled trials whose design includes children stratified by age groups and surgery type and a better description of the type of virtual reality software/hardware used are needed to adequately assess the effectiveness of virtual reality in reducing perioperative anxiety.
- Effectiveness of virtual reality should be assessed also for other secondary outcomes, such as pain, emergence delirium and postoperative maladaptive behaviours.

Keywords:

Anxiety, child, surgery, virtual reality, systematic review, meta-analyses

1. Introduction

Anxiety is a psychological condition associated with intense worry and/or fear in response to specific environmental stimuli and the absence of a proper adaptive reaction [Diagnostic And Statistical Manual Of Mental Disorders (DSM 2013)]. Anxiety during the perioperative period is a

major source of stress in most patients and may negatively impact the overall surgical outcome (Kain et al., 2006). Anxiety and stress can also impair postoperative recovery (Kain et al., 1996, Kain; Fischer et al., 2019), especially in vulnerable patients such as children, with long-term consequences that include maladaptive behaviours (Yuki & Daaboul, 2011; Naldan et al., 2018) and healthcare avoidance (Kotiniemi et al., 1997, Armfield et al., 2006; Byrne, 2008; Eijlers et al., 2020).

The most common anxiety triggers in the paediatric age group are fear of the unknown, pain (Wollin et al., 2004) and parental separation (Kain et al., 1996; Lee et al., 2013), all of which peak during the induction of general anaesthesia (Chorney & Kain, 2009; Fortier et al., 2010). Anxiety can also increase perceived pain and fear, thus causing the patients to avoid situations and places that have given rise to these sensations (Gatchel et al., 2007). The proper monitoring of anxiety (Fortier et al., 2010) during the perioperative period can contribute to a positive impact on the postoperative outcome with respect to pain control (Kain et al., 2006) as well as the avoidance of emergence delirium and maladaptive behavioural changes, including nightmares, enuresis, separation anxiety and eating disorders (Kain et al., 2004; Aouad et al., 2005, Kain et al., 2006).

Preoperative anxiety in children is currently managed using benzodiazepine premedication and non-pharmacological therapies such as distraction, a preoperative tour of the operating room and parental presence until the time of anaesthesia induction (Manyande et al., 2015). However, studies have shown that the administration of anxiolytics and opioid analgesics during the pre- and post-operative periods, respectively, are not free of risks and side effects (Cravero et al., 2019). By contrast, the use of non-pharmacological therapies for pain management offers a number of advantages, especially in paediatric patients. Other advantages include their low cost and their particularly good acceptance by children (Benini et al., 2010).

Distraction is one of the most commonly used non-pharmacological therapies; its effectiveness reflects the fact that if the distraction is sufficiently engaging and attractive the person's attention will shift away from the painful stimulus, leading to a reduction in pain (Sander Wint et al., 2002). For example, playing a video game that requires high cognitive engagement and attention to the challenges and difficulty of the game can progressively increase pain tolerance through a greater activation of the parasympathetic nervous system (Fairclough et al., 2020).

Virtual reality is a digital simulation of a computer-generated situation or environment where orientation and three-dimensional interaction are possible (Eijlers et al., 2019) by means of extremely sophisticated interfaces. It can be non-immersive or immersive. Non-immersive virtual reality reproduces a three-dimensional environment using devices with traditional graphics such as a computer monitor, television or video projector (Robertson et al., 1993). Immersive virtual reality

uses a headset or visor and motion-tracking systems to achieve a sense of complete isolation from the surrounding environment and of being truly immersed in and surrounded by the simulated world (Gupta 2017). The cognitive and sensory immersion experienced during a virtual reality-based video game thus offers a highly innovative non-pharmacological therapy for pain management.

A correlation between greater immersion/distraction and therefore a reduction in pain due to reduced pain perception has been demonstrated in different studies. Hoffman et al. (2004) showed that a decrease in pain intensity and therefore its degree of unpleasantness reduced autonomic activation as well as the motivation for escape or avoidance behaviours while Gold et al. (2005) found that virtual reality was able to reduce pain by modulating both the sensory (i.e.: touch, auditory, visual) and the emotional aspects of pain processing, thus producing analgesia. Moreover, in addition to its use as an active distraction technique, virtual reality can be used to explain/illustrate medical procedures to patients, further reducing their perioperative anxiety (Won et al., 2017; Riva, 2005; Gorini & Riva, 2008). Thus, by reducing the need for sedatives and anxiolytics, virtual reality also lowers the overall risks associated with sedation. In the paediatric setting, virtual reality can be introduced as a playful distraction technique (Eijlers et al., 2019) since children easily immerse themselves in virtual play (Weisberg, 2015). The inclusion of game elements in educational contexts (gamification) may facilitate children' s learning processes, including with respect to a medical procedure.

In the management of pain and anxiety in adults and children, virtual reality has been used in the treatment of oncology patients and patients with severe burns (Gupta 2017; Eijlers et al., 2019; Iannicelli et al., 2019), in the emergency room and during vaccinations (Arane et al., 2017; Eijlers et al., 2019). A recent meta-analysis determined that virtual reality was effective in reducing anxiety and pain in children undergoing medical procedures (Eijlers et al., 2019). In another study, virtual reality was successfully used in the operating room for simulations and in training activities (Khor et al., 2016).

The significant impact of anxiety on both the perception of pain (Tang & Gibson, 2005) and other postoperative outcomes, such as emergence delirium and maladaptive behaviours, in children undergoing surgery is well established. However, little is known about the effectiveness of virtual reality in reducing anxiety in paediatric patients during the perioperative period. Thus, in this review we evaluated the effectiveness of virtual reality in the management of paediatric anxiety during the perioperative period, including whether virtual reality improves anxiety-related postoperative outcomes such as pain, emergence delirium and postoperative maladaptive behaviours.

2. Methods

2.1. Design

Both a systematic review and a meta-analysis of randomised controlled trials (RCTs) were performed according to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions Section 8.5 (Higgins et al., 2019), in accordance with the Cochrane Effective Practice and Organisation of Care (EPOC, 2017). The results are reported as prescribed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist [PRISMA (Page et al., 2020)]. The study protocol was registered with the PROSPERO register, number (blinded for Referee), available at (blinded for Referee).

2.2. Search strategy

A systematic search was performed in the Medline (through PubMed), SCOPUS, Web of Science, Ovid MEDLINE and CINAHL (through EBSCOhost) databases from January to June 2021 using combinations of Medical Subject Headings (MeSH) and free text terms. Key search terms included: child, virtual reality, anxiety, preoperative anxiety, surgery, operating room. Table 1 shows the full search strategy used for the four databases. In addition, the references list of the included studies were reviewed for articles not retrieved in the initial search. There was no restriction on the date of publication (Savoie et al., 2003), but the publication languages were restricted to English and Italian.

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) RCTs, (ii) studies investigating the efficacy of virtual reality in the management of anxiety during the perioperative period, either as a primary or a secondary outcome; (iii) studies referring to paediatric inpatients < 19 years of age and including patients in the following age groups: pre-school (4–5 years), school (6–12) and adolescents (13–19) who participated in perioperative virtual reality for elective surgery conducted under general anaesthesia. Studies that met the following criteria were excluded: (i) carried out in non-operative settings; (ii) populations of adult or paediatric patients not undergoing elective surgery requiring general anaesthesia; (iii) including paediatric patients of other age groups (neonates, infants); (iv) including paediatric patients who received anxiolytic premedication or who had been diagnosed with certain cognitive impairments (psychiatric disorders, autism spectrum disorder); (v) investigating the effects of virtual reality in which anxiety was not a primary or secondary outcome and (vi) derived from the grey literature, reviews, meta-analysis or single case reports.

2.4. Screening

Two researchers (NV, VS) acting independently of each other initially screened all titles and abstracts of potentially relevant articles, deleting duplicated and irrelevant studies. The two authors then assessed the full text of all relevant articles using the sections “General Information” and

"Eligibility" of the Cochrane Data collection form (EPOC, 2017). Disagreements relating to article inclusion were resolved through a discussion with a third author (DC or GC) to reach a final consensus.

2.5. Inter-rater agreement

Inter-rater agreement between the two authors (NV, VS) for full-text selection was quantified with Cohen's Kappa (K), that was interpreted as follows (Altman, 1991): $k < 0.20$ *"poor"*, $0.21 < k < 0.40$ *"fair"*, $0.41 < k < 0.60$ *"moderate"*, $0.61 < k < 0.80$ *"good"*, $0.81 < k < 1.00$ *"very good"*.

2.6. Quality assessment

The included studies were assessed for quality and risk of bias by two independent researchers using the approach suggested in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019), which considers nine standard criteria: random sequence generation, allocation concealment, similar baseline outcome measurement, similar baseline characteristics, incomplete outcome data, knowledge of the allocated interventions adequately prevented during the study, and protection against contamination, selective outcome reporting and other risks of bias. The risk of bias was assessed using the following scoring: 'low risk of bias', in which plausible bias was unlikely to have altered the results; 'unclear risk of bias', in which plausible bias could raise doubt about the results and a 'high risk of bias', in which plausible bias could seriously weaken confidence in the results (Higgins et al., 2019). The methodological quality was evaluated with the Delphi list (Verhagen et al. 1998) to establish internal validity, external validity, and statistical aspects. This scale contains 9 items (1. Treatment allocation a) Was a method of randomization performed?; 2. Treatment allocation b) Was the treatment allocation concealed?; 3. Were the groups similar at baseline regarding the most important prognostic indicators?; 4. Were the eligibility criteria specified?; 5. Was the outcome assessor blinded?; 6. Was the care provider blinded?; 7. Was the patient blinded?; 8. Were point estimates and measures of variability presented for the primary outcome measures?; 9. Did the analysis include an intention-to-treat analysis?). Each item of the list can be evaluated as satisfactory (yes: scored 1) or non-satisfactory (no: scored 0). For our assessment, only item 7 was omitted, as it is impossible to be blinded due to the nature of intervention. For this reason, the maximum possible score for studies in this review was 8. Both quality assessment and risk of bias were conducted by two researchers (MT, VS) and any disagreements were resolved by a third researcher (DC).

2.7. Data extraction

The data extracted from each selected article included study author(s), year of publication, journal, study design, objective and outcomes, setting, participants, assessment and intervention tools and the main findings. Each study was independently extracted by one researcher (NV) and validated by

another (VS) using an adapted version of the sections "Population and settings", "Methods", "Participants" and "Outcomes" of the Cochrane Data collection form (EPOC, 2017).

2.8. Data synthesis

The total effect and heterogeneity indexes were estimated using Stata v12 (StataCorp., 2011), with adoption of the "metaan" package (Kontopantelis & Reeves, 2010). The random-effects models were constructed to incorporate an estimation of heterogeneity in the weighting (Harris et al., 2008) according to the most recent literature (Veroniki et al., 2019; Kontopantelis & Reeves, 2010). Random-effect estimates were based on the effect size calculation from each study and the total estimate of the effect size. The overall effect was estimated by adopting the Profile Likelihood (PL) random-effects model (Kontopantelis & Reeves, 2010).

Heterogeneity was determined using the Q-statistic in the χ^2 distribution and the p-value (Hoaglin, 2016): a significant p-value indicated that heterogeneity could affect the results. Since the Q-statistic must be interpreted with caution, especially if not significant, heterogeneity was further assessed by calculating the I^2 statistic (Higgins et al., 2019). According to the Cochrane standards, heterogeneity is not important if I^2 ranges from 0% to 40%, moderate from 30% to 60%, substantial from 50% to 90% and considerable from 75% to 100% (Higgins et al., 2019). The τ^2 statistic was also determined, as an estimate of the amount of variation between the included studies. Studies that were too heterogeneous in the measurement of their primary outcomes such that the results could not be pooled for the meta-analysis were summarised narratively.

Publication bias was assessed by performing the funnel plot. A funnel plot visually represents the estimation of the treatment's effect in the studies included in a meta-analysis: if a publication bias exists, the funnel plot is affected by an asymmetrical appearance and the meta-analysis could overestimate the treatment's effect (Sterne & Harbord, 2004). The "metafunnel" package was adopted to generating the funnel plot in Stata v12 (StataCorp., 2011; Sterne & Harbord, 2004).

3. Results

3.1. Study selection

The electronic database search yielded a total of 2588 articles. Following the removal of duplicated records, 1736 titles and abstracts were screened; a further 1725 articles were excluded because they did not meet the inclusion criteria. The eleven remaining eligible studies were assessed for eligibility and seven were included in the systematic review (Eijlers, et al., 2019b; Ryu, et al., 2017; Jung et al., 2020; Park et al., 2019; Ryu et al., 2018; Ryu et al., 2019; Dehghan et al., 2019). The search and screening procedures are summarised in the PRISMA flow diagram (Fig. 1).

3.2. Characteristics of the included studies

Table 2 presents the main characteristics and results of the seven included studies, which were conducted between 2017 and 2019, mainly in Asia (five studies) (Ryu et al., 2017, Park et al., 2019; Ryu et al., 2018; Ryu et al., 2019; Dehghan et al., 2019), Europe (Eijlers et al., 2019b) and in the USA (Jung et al., 2020).

All of the included studies were monocentric RCTs, with only one having a Salomon four-group design (Dehghan et al., 2019), and all compared the intervention group of children undergoing virtual reality with the usual care group, although details of the latter were not provided. Anxiety levels in children undergoing surgery were assessed using the Modified Yale Preoperative Anxiety Scale (mYPAS), with the exception of the study by Dehghan et al. (2019b), which used the Yale Preoperative Anxiety Scale questionnaire. Six studies compared the intervention group with the control group both at baseline and during anaesthesia induction; Ryu et al. (2017) assessed anxiety levels in both groups only before anaesthesia.

The patients ranged in age from 4 to 12 years, with sample sizes between 40 and 200. Virtual reality intervention was provided with the same device (Galaxy S6®, Samsung) in three studies (Ryu et al., 2017; Jung et al., 2020; Park et al., 2019; Ryu et al., 2019) but with different devices in the other studies, although all used facial visors designed specifically for children.

3.3. Agreement

Inter-rater agreement for full text selection between authors (NV, VS) was "good" ($K = 0.737$; $p = 0.016$).

3.4. Quality assessment of the studies included in the meta-analysis

The methodological quality varied among the seven studies included in the review. In particular, the quality score of the included studies was reduced because they did not fully meet the following criteria: treatment allocation concealment (Eijlers et al., 2019b; Ryu et al., 2018; Park et al., 2019; Dehghan et al., 2019), groups similar at baseline regarding the most important prognostic indicators (Ryu et al., 2017), blinding of the care provider (Ryu et al., 2017; Ryu et al., 2018; Jung et al., 2020; Dehghan et al., 2019), inclusion of intention-to-treat analysis (Ryu et al., 2017; Ryu et al. 2018; Ryu et al. 2019) (Tab. 2). The overall risk of bias for the studies included in the meta-analysis was low. Jung et al. (2020) did not fully meet the following criteria: knowledge of the allocation interventions and the random sequence generation was unclearly reported; while for Ryu et al. (2018) there is uncertain whether similar baseline characteristics were adequately prevented during the study. Ryu et al. (2017) presented high risk of bias for similar baseline outcome measurement and uncertain similar baseline characteristics (Fig. 2).

3.5. Virtual reality and anxiety management: quantitative data synthesis

The effect size for anxiety was determined in six (Eijlers et al., 2019b; Jung et al., 2020; Park et al., 2019; Ryu et al., 2019; Ryu et al., 2018; Ryu et al., 2017) of the seven studies included in the review. A study was excluded from the quantitative meta-analysis because anxiety was measured using a different instrument, the scores did not report all the necessary information to performing a quantitative synthesis and the methods were affected by biases in random sequence generation, allocation concealment, baseline similar characteristics and groups' allocation (Dehghan et al., 2019).

Our findings support the effectiveness of virtual reality in reducing anxiety in paediatric patients undergoing surgery: the oveall effect size was negative with 95% confidence interval below 0, indicating the effectiveness of VR in reducing the outcome measure (PL=-0.341, 95% confidence interval [95%CI]: −0.620 to −0.107). Table 3 reports the detailed effect size measures for each study included and the overall meta-analytic effect size with the 95%CIs.

Heterogenity indexes that were non-significant (Q=9.49, p=0.091, df=5) or not important (I^2=38.64%, confidence interval [95%CI]: 0.00-75.62), the absolute value of heterogeneity was low (τ^2=0.029, confidence interval [95%CI]: 0.001-0.232) (Higgins & Green, 2008). Figure 3 reports the forest plot and the heterogeneity indexes.

The funnel plot indicated an acceptable symmetry in studies' distribution along the overall effect line and it supported that the meta-analysis outcome was not affected by publication bias (Figure 4).

3.6. Effects of virtual reality on secondary outcomes: qualitative synthesis

3.6.1. Pain management

Of the seven included studies, only Eijlers et al. (2019b) measured postoperative pain using three different instruments: (i) the self-reported Six-Faces Revised Faces Pain Scale (FPS-r) at T4 (postoperatively) and T5 (at home, 2 weeks after surgery); (ii) Face, Legs, Activity, Cry and Consolability (FLACC) at T4, in which a blinded recovery nurse assessed the intensity of the children's pain and (iii) the Parent's Postoperative Pain Measure (PPPM), in which parents assessed their child's pain at T5. The results showed no differences in pain levels between the intervention group and the usual care group based on assessments using the FPS-r (p=0.699; p=0.454 at T4 and T5, respectively), FLACC (p=0.669) and PPPM (p=0.410).

3.6.2. Compliance

The children's compliance during anaesthesia induction was assessed as a secondary outcome in four studies (Ryu et al., 2017; Jung et al., 2020; Park et al., 2019; Ryu et al., 2018), all of which used the Induction Compliance Checklist (ICC). The results differed between studies. Ryu et al. (2017) and Ryu et al. (2018) reported lower ICC scores, and thus better behavioural compliance, in

the intervention group than in the usual care group during the intraoperative period ($p<0.01$; $p=0.038$, respectively). However, Park et al. (2019) and Jung et al. (2020) found no significant difference between the two groups ($p=0.722$; $p=0.12$, respectively).

3.6.3. Behavioural disturbances

Four of the seven studies examined behavioural disturbances during the surgical procedure (Eijlers et al., 2019b; Ryu et al., 2017; Ryu et al., 2018; Ryu et al., 2019), using different instruments of assessment. Ryu et al. (2017) and Ryu et al. (2018) used the procedural behaviour rating scale (PBRS) during the induction of general anaesthesia, while Ryu et al. (2019) used the Post-Hospitalization Behaviour Questionnaire for Ambulatory Surgery (PHBQ-AS), calling the child's parent on postoperative days 1 and 14 days. Eijlers et al. (2019b) used the Child Behaviour Checklist (CBCL), completed by the patients' parents, during the preoperative period. In general, postoperative behavioural disturbances did not differ between the two groups, except in the study by Ryu et al. (2017), which found lower PBRS scores for children in the intervention group than in in the usual care group ($p=0.010$).

3.6.6. Emergence delirium

The Paediatric Anaesthesia Emergency Delirum (PAED) scale was used postoperatively by Eijlers et al. (2019) and Ryu et al. (2019). In neither was there a difference between the two groups in the incidence and severity of emergence delirium symptoms (both $p>0.05$; Table 2).

4. Discussion

The aim of this systematic-review and meta-analysis was to ascertain the effectiveness of virtual reality in reducing anxiety, pain, compliance, behavioural disturbances and emergence delirium in children undergoing elective surgery. The primary outcome (anxiety) was assessed based on five studies, which showed that virtual reality is effective in reducing anxiety scores in children during the induction of general anaesthesia. The results are in line with those of Eijlers et al. (2019), who in their review of children undergoing medical procedures reported a large effect size for the intervention group and thus the benefits of virtual reality intervention in reducing pain and anxiety. Only one of the included studies (Eijlers et al., 2019b) reported no effect of virtual reality intervention in anxiety reduction. Those authors explained this result by the fact that both intervention group and usual care group patients received routine care, which emphasises patient comfort, in line with the patient- and family-centred care concept (Kuhlthau et al., 2011). Thus, environmental factors, such as the availability of appropriate games and toys and parental presence, are important factors in reducing anxiety in paediatric patients, particularly younger children, in whom parental separation is likely to be a source of anxiety and stress (Comparcini et al., 2018). In

addition, the authors excluded more complex procedures and many of the children (n=23) prematurely removed the virtual reality headset, thus ending the intervention (Eijlers et al., 2019b). These elements may have affected anxiety levels and other outcome measures.

In our assessment of secondary outcomes, analysed as qualitative data, we found no consensus among authors on the efficacy of virtual reality in improving children' s compliance (Ryu et al., 2017; Jung et al., 2020; Park et al., 2019; Ryu et al., 2018) or in reducing behavioural disturbances (Eijlers et al., 2019b; Ryu et al., 2017; Ryu et al., 2018; Ryu et al., 2019). However, comparisons among the included studies were difficult because of differences in the instruments used to assess behaviour and in the timing of the perioperative assessment. Moreover, the only RCT that investigated pain as a secondary outcome (Eijlers et al., 2019b) did not find a beneficial effect of virtual reality on pain. Nevertheless, among children undergoing the most painful type of surgery, less rescue analgesia was needed by those in the intervention group than in the control one. The authors suggested that the lack of a strong game design compromised the virtual reality intervention (Eijlers et al., 2019b). It may be that, in contrast to a simple virtual tour of the operating room, the inclusion of appealing game elements in virtual reality (Jung et al., 2020; Ryu et al., 2018) would ensure that children are fully engaged in a fun activity (Eijlers et al., 2019b; Ryu et al., 2017; Park et al., 2019; Ryu et al., 2019) and thus improve all outcomes. Further studies are needed that examine the effects of gamification in virtual reality on perioperative outcomes in paediatric patients undergoing elective surgery requiring general anaesthesia.

Nonetheless, it may be difficult to discriminate between the effects of virtual reality and other forms of distraction. Moreover, in the included studies, details on the provision of routine or usual care were not reported. Also, the intervention in the intervention group differed among studies regarding duration, the virtual reality device, the type of immersive approach (hardware and software) and the type of pre-intervention education or training.

4.1. Overall assessment of study quality

The included studies varied in quality. Blinding of the participants was not applicable since the intervention involved the use of a virtual reality device, generally a headset or a visor. Assessors' knowledge of the allocated interventions was adequately prevented during the study except in Jung et al. (2020) and Dehghan et al. (2019). In the latter, allocation concealment was not reported, as neither random sequence generation nor the similarity of the baseline characteristics of the groups were described Dehghan et al. (2019). Ryu (2017, 2019) did not compare the data of the intervention group and control group at baseline.

4.2. Review strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis of the efficacy of virtual reality during the perioperative period in paediatric patients undergoing elective surgery, specifically with respect to anxiety levels, pain, emergence delirium, behavioural disturbances and compliance.

However, several limitations that may have impacted the results should be noted. First, effect sizes for self-reported anxiety could be determined in only five studies (Eijlers et al., 2019; Jung et al., 2020; Park et al., 2019; Ryu et al., 2018; Ryu et al., 2019; Dehghan et al., 2019), thus indicating the need for greater methodological rigor to improve future reviews and meta-analyses. Second, the included studies neglected important aspects such as the use training programmes before the intervention, the different types of software and hardware used in the virtual reality devices, the characteristics of the patients (i.e. age, sex, temperament, attitudes towards virtual reality, anxiety sensitivity) and the relationship between parents/guardians and the child, which could affect the child's ability to cope with surgery. In addition, the limited number of relevant RCTs may have influenced the results of the review. We should also consider the heterogeneity of control conditions in terms of type and nature of care provided in the control group, that were not always described by authors in detail. Also, most of the articles included in this review (Park et al. 2019; Ryu et al. 2017; Ryu et al. 2018; Ryu et al. 2019) were conducted in the same Country (Korea); this aspect should be considered when comparing the results of studies conducted in different health systems around the world. In fact, we have to recognize that the processes of health and illness in the realities of clinical practice should be analysed also from a transcultural perspective (Langdon & Wiik, 2010); in this vein, it is important to take into account the peculiarities that do not derive from biological differences, but from differences of a social-cultural nature. Therefore, issues related to health and patients' experiences of disease should be considered from the point of view of the specific socio-cultural contexts in which they occur. These issues make difficult to compare results among studies. We should also consider that some databases (Embase and PsycInfo) were not consulted, with a potential bias to not identify as many eligible studies as possible.

4.3. Implications for practice and research

Virtual reality can be considered an effective non-pharmacological treatment to manage children's anxiety during the preoperative period, a clinically important finding because of the side effects associated with analgesic drugs. Moreover, the use of virtual reality to manage anxiety and pain in children undergoing elective surgery with virtual reality could improve children's overall hospital experience, by increasing cooperation with healthcare workers before surgery and by preventing possible consequences (e.g., post-traumatic stress disorder) (Gold & Mahrer, 2018) that could

adversely affect future hospitalisations. Also, virtual reality is relatively simple and easy to use technology to apply in clinical practice, not requiring logistic efforts or higher costs for healthcare services. However, we should also consider that not all patient would be eligible for this technology (eg. neonates, children suffering claustrophobia or affected by Attention-Deficit/Hyperactivity Disorders). In general, virtual reality, ensuring emotional mental well-being (through anxiety reduction) could positively impact on hasting recovery, playing a potential helpful role for those nurses caring for children and their families during the difficult steps of the perioperative process through the operating room.

The focus of future studies could include children stratified by various age groups and undergoing major surgery and/or emergency procedures, as they are potentially exposed to higher levels of perioperative anxiety than children undergoing minor/elective surgery. Other potentially important factors are the timing and optimal duration of virtual reality exposure during the perioperative period (i.e. at baseline, prior to the induction of general anaesthesia and postoperatively). Collaborations with virtual reality designers to develop applications specifically tailored for paediatric patients and adapted according to age group (Caffarelli et al., 2020) should also be considered.

Finally, the role of virtual reality in reducing postoperative pain is unclear, since its effect has thus far been investigated in only one RCT; further well-designed studies are therefore needed. The demonstration of a positive effect on anxiety in terms of children's pain perception during the postoperative period may translate into better postoperative outcomes, such as reductions in morbidity, hospitalisation times and related health costs. Furthermore, parents and guardians have not been adequately surveyed and there are many related biases in the literature. Two of the included studies (Jung et al., 2020; Park et al., 2019) evaluated both anxiety and the satisfaction of parents/guardians with the virtual reality procedure, whereas Ryu et al. (2017) and Ryu et al. (2018) evaluated only parental satisfaction and Eijlers et al. (2019) only anxiety. Further studies that include parents/guardians will provide a better understanding of the perioperative experience of paediatric patients.

5. Conclusion

In conclusion, our systematic review and meta-analysis showed that children undergoing elective surgery benefit from virtual reality as a distraction method that reduces anxiety. A consensus for secondary outcomes of pain, behavioural disturbances, emergence delirium and compliance could not be obtained.

Research that uses the same methods, instruments and devices is needed to compare the efficacy of virtual reality and to better understand its applications in clinical practice.

Declaration of Competing Interest

None.

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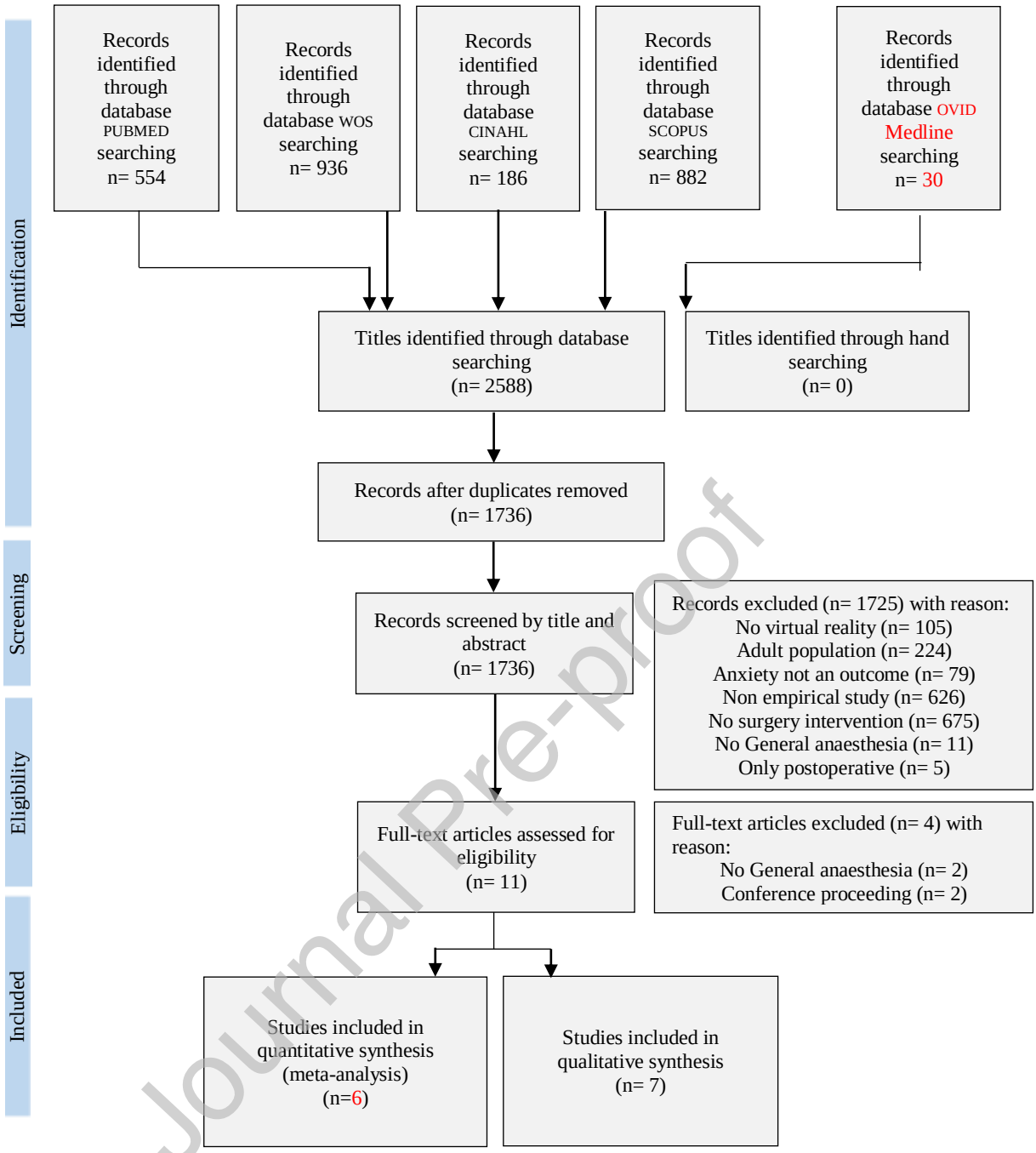

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of study selection.

Fig. 2. Assessment of risk of bias using the Cochrane Risk of Bias Tool (Higgins et al., 2019).

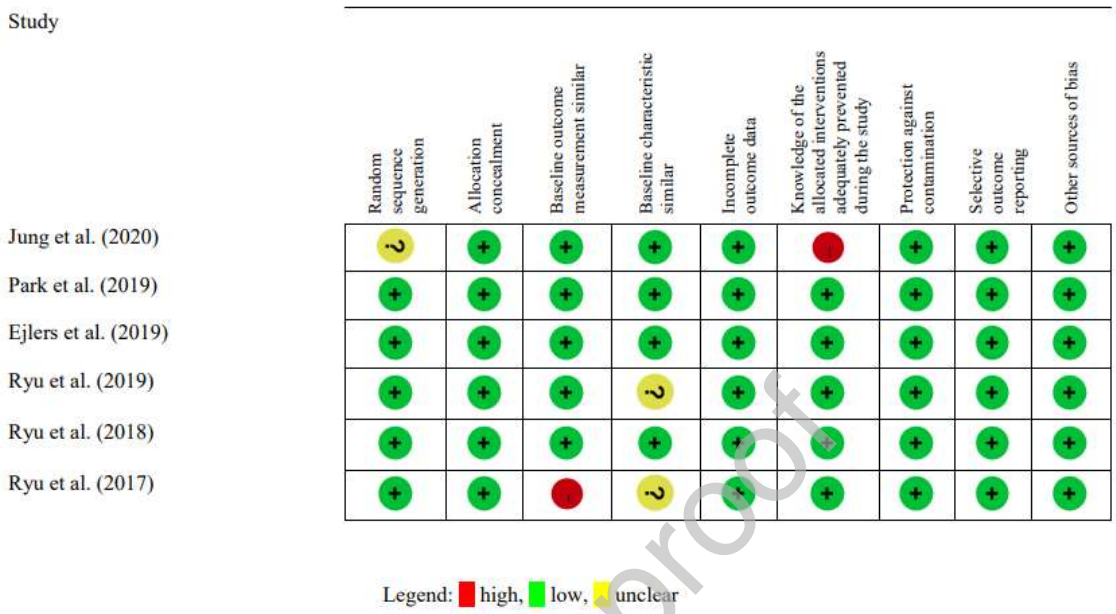

Fig. 3. Meta-analysis of the effectiveness of VR in reducing anxiety: forest plot and heterogeneity indexes (Q, I^2, τ^2).

(Negative values represent a favourable effect of VR compared to the standard)

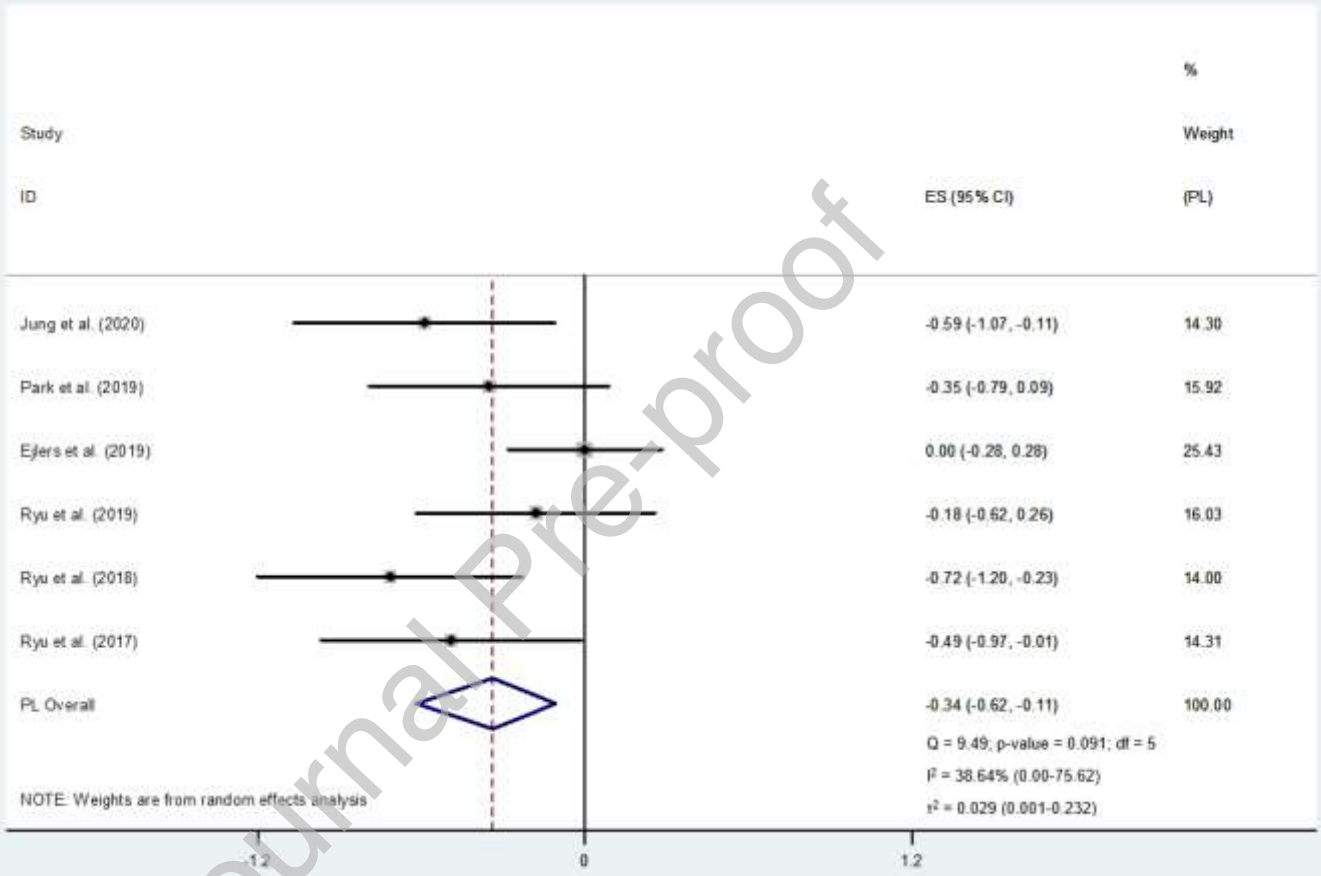

Fig. 4. Publication bias assessment: funnel plot.

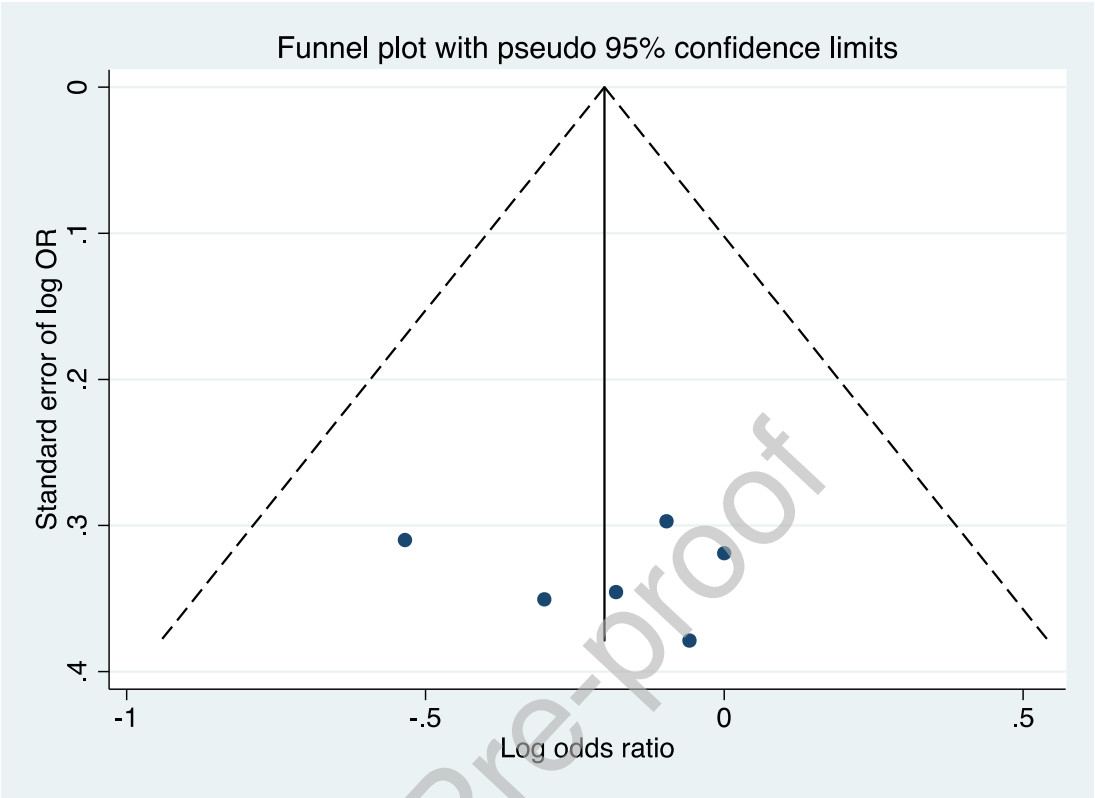

Table 1. Literature search of the electronic databases.

Database	Search strategy	Number
PUBMED	(("Child"[Mesh] AND "Child, Preschool"[Mesh]) AND ("Pain"[Mesh] OR "Acute Pain"[Mesh] OR "Pain Management"[Mesh] OR "Pain, Procedural"[Mesh])) AND ("Virtual Reality"[Mesh] OR "Virtual Reality Exposure Therapy"[Mesh])	15
PUBMED	((Virtual Reality) AND ((child*) OR (pediatric*)) AND (adolescent) AND ((pain) OR (anxiety) OR (hospital*) OR (therap*) AND (operating room))	1
PUBMED	((Virtual Reality) AND ((child*) OR (pediatric*)) AND ((pain) OR (hospital*) OR (therap*) OR (anxiety))) AND (adolescent)	299
PUBMED	((((virtual reality) AND ((child*) OR (pediatric*)) AND ((pain*) AND (hospital*) AND (preoperative anxiety))) AND (surgery)))	9
PUBMED	((Virtual Reality) AND ((child*) OR (pediatric*)) AND ((pain) OR (hospital*) OR (therap*) AND (surgery) OR (operating room) OR (anxiety)))	358
PUBMED	(((pediatric[Title/Abstract]) AND (virtual reality[Title/Abstract])) AND (perioperative[Title/Abstract])) AND (distraction)	1
PUBMED	virtual reality AND pediatric AND surgery AND distraction	27
SCOPUS	(TITLE-ABS-KEY(virtual reality) AND TITLE-ABS-KEY((child*) OR (pediatric*)) AND TITLE-ABS-KEY((pain*) OR (hospital*) OR (therap*) OR (anxiety)) AND (EXCLUDE (SUBJAREA,"MATH") OR EXCLUDE (SUBJAREA,"BIOC") OR EXCLUDE (SUBJAREA,"ARTS") OR EXCLUDE (SUBJAREA,"PHYS") OR EXCLUDE (SUBJAREA,"AGRI") OR EXCLUDE (SUBJAREA,"CENG") OR EXCLUDE (SUBJAREA,"MATE") OR EXCLUDE (SUBJAREA,"ENER") OR EXCLUDE (SUBJAREA,"ENVI") OR EXCLUDE (SUBJAREA,"BUSI") OR EXCLUDE (SUBJAREA,"CHEM") OR EXCLUDE (SUBJAREA,"IMMU") OR EXCLUDE (SUBJAREA,"VETE")) AND (EXCLUDE (LANGUAGE,"French") OR EXCLUDE (LANGUAGE,"Turkish")) AND (EXCLUDE (LANGUAGE,"Portuguese") OR EXCLUDE (LANGUAGE,"Spanish") OR EXCLUDE (LANGUAGE,"German") OR EXCLUDE (LANGUAGE,"Russian") OR EXCLUDE (LANGUAGE,"Chinese") OR EXCLUDE (LANGUAGE,"Polish") OR EXCLUDE (LANGUAGE,"Czech") OR EXCLUDE (LANGUAGE,"Japanese")))	885
SCOPUS	(TITLE-ABS-KEY(virtual reality) AND TITLE-ABS-KEY((child*) OR (pediatric*)) AND TITLE-ABS-KEY((pain*) OR (hospital*) OR (therap*) OR (anxiety)) AND (surgery) AND (EXCLUDE (SUBJAREA,"MATH") OR EXCLUDE (SUBJAREA,"BIOC") OR EXCLUDE (SUBJAREA,"ARTS") OR EXCLUDE (SUBJAREA,"PHYS") OR EXCLUDE (SUBJAREA,"AGRI") OR EXCLUDE (SUBJAREA,"CENG") OR EXCLUDE (SUBJAREA,"MATE") OR EXCLUDE (SUBJAREA,"ENER") OR EXCLUDE (SUBJAREA,"ENVI") OR EXCLUDE (SUBJAREA,"BUSI") OR EXCLUDE (SUBJAREA,"CHEM") OR EXCLUDE (SUBJAREA,"IMMU") OR EXCLUDE (SUBJAREA,"VETE")) AND (EXCLUDE (LANGUAGE,"French") OR EXCLUDE (LANGUAGE,"Turkish") OR EXCLUDE (LANGUAGE,"Portuguese") OR EXCLUDE (LANGUAGE,"Spanish") OR EXCLUDE (LANGUAGE,"German") OR EXCLUDE (LANGUAGE,"Russian") OR EXCLUDE (LANGUAGE,"Chinese") OR EXCLUDE (LANGUAGE,"Polish") OR EXCLUDE (LANGUAGE,"Czech") OR EXCLUDE (LANGUAGE,"Japanese")))	204
WOS	TS=((virtual reality) AND ((child*) OR (pediatric)) AND ((PAIN*) AND (hospital*) AND (preoperative anxiety) AND (surgery) OR (operative room)))	8
WOS	TS=((Virtual Reality) AND ((child*) OR (pediatric*)) AND ((pain) OR (hospital*) OR (therap*) OR (anxiety)))	932
CINAHL	((Virtual Reality) AND ((child*) OR (pediatric*)) AND ((pain) OR (hospital*) OR (therap*) AND (surgery) OR (operating room) OR (anxiety)))	191
CINAHL	(virtual reality or vr) AND (pediatric or child or children or infant or adolescent) AND (pain management or pain relief or pain control or pain reduction) AND anxiety AND (surgery or operation or surgical procedure or surgical treatment or operative)	5
CINAHL	virtual reality AND (child or pediatric or paediatric or children) AND anxiety AND (surgery or operating room)	7
CINAHL	((Virtual Reality) AND ((child*) OR (pediatric*)) AND (adolescent) AND ((pain) OR (anxiety) OR (hospital*) OR (therap*) AND (operating room))	37
OVID Medline	("virtual reality" and (child* or pediatric*) and hospital* and "preoperative anxiety" and surgery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5

OVID Medline	("virtual reality" and (child* or pediatric*) and (anxiety or pain) and ("operating room" or surg*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	30
OVID Medline	("virtual reality" and child* and anxiety and surgery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	16

Table 2. Characteristics and main results of the included studies on the effectiveness of virtual reality on pain in paediatric patients undergoing surgical procedures (n = 7).

Author(s) (year) ***Journal***	**Study Design**	**Objective and outcomes**	**Setting, Country and study period**	**Participants**		**Location of VR session**	**Type and nature of the intervention. (Number of patients)**	**Control (number of patients)**	**Instruments and time points of outcome assessment**	**Main results**	**Quality score**
				n	**Age**						
Eijlers et al. (2019)* *European Journal of Anaesthesiology*	Single-blind RCT.	***Aim*:** to evaluate virtual reality exposure in preparing children for elective inpatient surgery with respect to reducing anxiety, pain and emergence delirium. ***Primary outcome*:** anxiety during general anaesthesia induction. ***Secondary outcomes*:** pain; emergence delirium; behaviour; parental anxiety.	Sophia Children's hospital, Holland, March 2017 - October 2018.	191	4-12 y	In the holding area, before entering the operating room.	HTC Vive visor, monitor PC. Video virtual reality of the operating room in two versions (4–7 years) and (8–12 years). (N=94)	Usual care. (N=97)	***Anxiety:*** mYPAS at T1 (baseline) -T2 (holding area) -T3 (during induction of GA) VAS at T1–T2–T4 (postoperatively)–T5 (at home 2 weeks after surgery). ***Pain:*** FPS-r at T4–T5 FLACC at T4 PPPM at T5 ***Emergence delirium:*** PAED at T4 ***Behaviour child:*** CBCL at T1.	No significant differences were found at T1–T2–T3 in mYPAS scores and at T1-T2-T4 in VAS scores (all p>0.05). No difference in pain, emergence delirium, behaviour between groups (all p>0.05).	7

Ryu et al. (2017) *British Journal of Surgery*	RCT.	***Aim:*** to evaluate whether a virtual reality tour of the operating room reduced preoperative anxiety in children. ***Primary outcome*:** preoperative anxiety. ***Secondary outcomes:*** compliance and stressful behaviour during general anaesthesia induction; parental satisfaction after general anaesthesia induction.	Seoul National University Bundang Hospital, Korea, January - April 2017.	70	4-10 y	In a separate empty room 1 h prior to entering the operating theatre.	Samsung Gear headset and smartphone (Galaxy S6®; Samsung). VR video of the operating room (360°) and the perioperative process. (N= 34).	Standard information regarding the process of anaesthesia and surgery. (N= 35).	***Anxiety:*** mYPAS 30 min before anaesthesia induction (holding area). ***Compliance:*** ICC during general anaesthesia induction. ***Stressful behaviour:*** PBRS: during general anaesthesia induction.	The m-YPAS score was significantly lower in the virtual reality group than in the control group in the preoperative holding area before entering the operating room ($p<0.001$). During general anaesthesia induction: lower ICC ($p<0.001$) and PBRS ($p=0.010$) scores in VR group.	5
Jung et al. (2020)* *Pediatric Anesthesiology*	RCT parallel group study.	**Aim:** to determine whether immersive audiovisual distraction with a virtual reality headset during general anaesthesia induction in paediatric patients reduced preoperative anxiety. **Primary outcome:** preoperative	San Francisco Benioff Children's Hospital, University of California, USA, August 2018 - March 2019.	71	5-12 y	During induction of general anaesthesia in the operating room. (N=33)	Samsung Gear VR headset displayed interactive game (software ChariotVR) designed for paediatric preoperative use.	Standard medical care without any audiovisual devices. (N=37)	***Anxiety:*** m-YPAS at T0 (baseline) - T1 (entering the operating room) - T2 during induction of general anaesthesia. ***Compliance:*** ICC at T2.	The change in mYPAS scores from baseline to time of induction was significantly lower in the virtual reality group versus control group (0.0 [0.0–5.0] vs 13.3 [5.0–26.7]; $P < .0001$). In the mixed-effects model, the virtual	6

		anxiety. **Secondary outcomes:** compliance during general anaesthesia induction of general anaesthesia; parental perioperative anxiety; parental satisfaction.							reality group had an estimated 6.0-point lower mYPAS score (95% confidence interval [CI], 0.7–11.3; P = .03) at room entry than the No-virtual reality group, and a 14.5-point lower score (95% CI, 9.3–19.8; P < .0001) at induction versus control.	
Park et al. (2019)* *IEEE Journal of Biomedical and Health Informatics*	RCT.	**Aim:** to determine whether a parental co-experience of a preoperative virtual reality tour using a mirroring display further reduced preoperative anxiety. **Primary outcome:** preoperative anxiety. **Secondary outcomes:** parental anxiety and satisfaction; child complianc	Seoul National University Bundang Hospital, Korea, January - February 2018.	80 4-10 y	In a separate empty room 1 h prior to entering the operating room.	Samsung Gear Visor and smartphone (Galaxy S6®; Samsung), Samsung mirroring device Smart Mirroring 2.0 SE. Mirroring devices mirror the same content of the video onto a monitor display to provide the same tour to their parents. (N=40)	Virtual reality-guided tour of the operating theatre via a smartphone (Galaxy S6®, Samsung, Suwon, Korea) and a head mounted display (VR Gear®; Samsung) (N=40)	***Anxiety:*** m-YPAS at baseline - before induction of general anaesthesia. ***Compliance:*** ICC during induction of general anaesthesia.	Prior to the induction of general anaesthesia, the m-YPAS scores in the intervention group were significantly lower than those in the control group (28.3 [23.3-36.7] vs. 38.3 [23.3-44.2]; p = 0.025). No differences in ICC scores between the two groups (p=0.722).	7

		e.								
Ryu et al. (2018)* *Journal of Clinical Medicine*	RCT.	**Aim:** to evaluate whether gamification of the preoperative process using virtual reality gaming reduced preoperative anxiety in children. **Primary outcome:** preoperative anxiety. **Secondary outcomes:** compliance; stressful behaviour during general anaesthesia induction and parental satisfaction after general anaesthesia induction.	Seoul National University Bundang Hospital, Korea, February - April 2018.	70 4-10 y	In a separate empty room 1 h prior to entering the operating room.	Oculus Rift Headset, hand and finger motion controller - Leap motion controller. (N= 35).	Conventional mode of education about the preoperative process. (N= 35).	***Anxiety:*** m-YPAS at baseline and before induction of general anaesthesia. ***Compliance:*** ICC during induction of general anaesthesia. ***Stressful be*** general anaesthesia ***haviour child:*** PBRS: during induction of general anaesthesia.	Lower m-YPAS scores of the virtual reality group after the intervention (28.3 [23.3–36.7] vs. 46.7 [31.7–51.7]; p < 0.001). m-YPAS scores before and after the intervention were significantly different between the two groups (−22.5 vs. 0; p = 0.002). Better induction compliance in the intervention group (p=0.038).	5
Ryu et al. (2019)* *Pediatric Anesthesia*	RCT.	**Aim:** to determine whether an immersive virtual reality tour of the operating room reduced preoperati	Seoul National University Bundang Hospital, Korea, June - October 2017.	80 4-10 y	In a separate empty room 1 h prior to entering the operating room.	Visor Samsung Gear e smartphone (Galaxy S6®; Samsung). Virtual reality 360° immersive tour of the	Institution's standard preoperative educational procedure. (N= 42).	***Anxiety:*** m-YPAS at baseline and before GA induction. ***Emergence delirium child:*** PAED during PACU stay. ***Postoperative behaviour***	The incidence and severity of emergence delirium were similar in the two groups (p=0.773). Before	7

		ve anxiety and thus the incidence of emergence delirium. **Primary outcome:** incidence and severity of emergence delirium. **Secondary outcomes:** preoperative anxiety and postoperative behavioural disturbance.				operating room. (N= 41).		***disturbance:*** PHBQ-AS by calling child's parent on 1 and 14 days after surgery.	general anaesthesia induction, children in the virtual reality group had a significantly lower m-YPAS score than those in the control group (p = 0.022). There was no difference in postoperative behavioural disturbance between the two groups at 1 and 14 days after surgery (p=0.671 and p=0.329, respectively).	
Dehghan, Jalali & Bashiri (2019) *Perioperative Medicine*	RCT Salomon four group design.	**Aim:** to evaluate whether virtual reality reduced preoperative anxiety in children. **Primary outcome:** preoperative anxiety.	Kermanshah University of Medical Sciences, Iran. Period of data collection not specified.	40	6-12 y	Not specified.	Eyeglasses, headphones e PC monitor. A 5-min exposure to the operating room using virtual reality technology. (N= 20).	Touch and caress by parents of children prior to operation. (N= 20).	***Anxiety:*** Yale Preoperative Anxiety Scale questionnaire at baseline and post-test.	Significant reduction of preoperative anxiety in all subscales among the intervention group from baseline to post-test ($p<0.05$), except for apparent arousal domain.	5

*Studies included in the Meta-Analysis.

Table 3. Effect size, 95%CIs and weight (%) for each study included and overall effect of VR. (Negative values represent a favourable effect of VR compared to the standard)

Study	Effect	low 95%CI	high 95%CI	Weight (%)
Jung et al. (2020)	-0.591	-1.070	-0.111	14.30
Park et al. (2019)	-0.353	-0.795	0.089	15.92
Ejlers et al. (2019)	0.000	-0.284	0.284	25.43
Ryu et al. (2019)	-0.181	-0.620	0.258	16.03
Ryu et al. (2018)	-0.717	-1.204	-0.230	14.00
Ryu et al. (2017)	-0.493	-0.972	-0.014	14.31
Overall effect (pl)	-0.341	-0.620	-0.107	100.00