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Systematic Review and Meta-analysis of Virtual Reality in Pediatrics: Effects on Pain and Anxiety

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BACKGROUND: Medical procedures often evoke pain and anxiety in pediatric patients. Virtual reality (VR) is a relatively new intervention that can be used to provide distraction during, or to prepare patients for, medical procedures. This meta-analysis is the first to collate evidence on the effectiveness of VR on reducing pain and anxiety in pediatric patients undergoing medical procedures.
METHODS: On April 25, 2018, we searched EMBASE, MEDLINE, CENTRAL, PubMed, Web of Science, and PsycINFO with the keywords "VR," "children," and "adolescents." Studies that applied VR in a somatic setting with participants ≤21 years of age were included. VR was defined as a fully immersive 3-dimensional environment displayed in surround stereoscopic vision on a head-mounted display (HMD). We evaluated pain and anxiety outcomes during medical procedures in VR and standard care conditions.
RESULTS: We identified 2889 citations, of which 17 met our inclusion criteria. VR was applied as distraction (n = 16) during venous access, dental, burn, or oncological care or as exposure (n = 1) before elective surgery under general anesthesia. The effect of VR was mostly studied in patients receiving burn care (n = 6). The overall weighted standardized mean difference (SMD) for VR was 1.30 (95% CI, 0.68–1.91) on patient-reported pain (based on 14 studies) and 1.32 (95% CI, 0.21–2.44) on patient-reported anxiety (based on 7 studies). The effect of VR on pediatric pain was also significant when observed by caregivers (SMD = 2.08; 95% CI, 0.55–3.61) or professionals (SMD = 3.02; 95% CI, 0.79–2.25). For anxiety, limited observer data were available.
CONCLUSIONS: VR research in pediatrics has mainly focused on distraction. Large effect sizes indicate that VR is an effective distraction intervention to reduce pain and anxiety in pediatric patients undergoing a wide variety of medical procedures. However, further research on the effect of VR exposure as a preparation tool for medical procedures is needed because of the paucity of research into this field. (Anesth Analg 2019;129:1344–53)

KEY POINTS

- **Question:** Is virtual reality (VR) effective in reducing pain and anxiety in pediatric patients undergoing medical procedures?
- **Findings:** VR was most often used as a distraction method during medical procedures and was found to be significantly more effective in reducing pain (14 studies) and anxiety (7 studies), with large effect sizes, than care as usual (CAU).
- **Meaning:** VR can be used effectively as a distraction method in clinical practice, but more research is needed to establish evidence on VR exposure as a preparation tool for medical procedures.

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Medical procedures often evoke pain, distress, and anxiety.[1] Especially in children, these feelings not only severely affect comfort levels during medical procedures but are also associated with adverse consequences, such as attempts to escape,[2] poor recovery,[3] eating and sleeping disturbances,[3] and posttraumatic stress symptoms.[4] Furthermore, as pain and anxiety can lead to avoidance of health care,[5,6] interventions are needed to address pain and anxiety in pediatric patients.

Distraction is a commonly applied intervention during medical procedures. For example, the use of music[7,8] and movies[9,10] has been proven efficacious in reducing pain and anxiety. Virtual reality (VR) is a relatively new technique to provide distraction and might be more effective than traditional methods. VR consists of a computer-generated environment, in which orientation and 3-dimensional interaction are possible. This environment is projected right in front of the user's eyes via advanced head-mounted displays (HMDs), including a wide field of view and motion tracking systems.[11] VR can create full immersion, which is a feeling of presence in the virtual environment.[11,12] Importantly, more immersion is related to more pain reduction, because

less attention is available for pain perception.[13,14] VR is especially engaging for children, as they often become truly captivated by imaginative play.[15] Beyond providing distraction, VR can also alleviate pain and anxiety by providing exposure. Recently, VR exposure has been applied in a more preventive manner, to make patients feel at ease and increase their familiarity with the medical procedures and environments.[16,17] This preprocedural application of VR has not been thoroughly evaluated yet.

While the amount of research investigating the effect of VR on alleviating pain and anxiety has increased over the past years, studies are often small and encompass a wide variety of medical procedures. This emphasizes the need for a systematic evaluation of VR in pediatric populations. Although some reviews are available on the effectiveness of VR on pain,[18,19] the effectiveness on anxiety has received little attention. This is remarkable, because anxiety can intensify pain.[20] Only 1 meta-analysis is available on VR interventions,[21] but no meta-analysis has specifically focused on children. This distinction is important, because children are potentially even more affected by discomfort of medical procedures and might experience VR differently than adults.

In this meta-analysis, we will collate evidence on the effectiveness of VR as either a distraction or an exposure tool, compared to standard care, on pain and anxiety in pediatric patients undergoing medical procedures.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the reporting of meta-analyses of randomized controlled trials (RCTs).[22]

Selection Criteria

Studies reporting on the effect of VR on reducing pain and/or anxiety in pediatric patients ≤21 years of age undergoing medical procedures were considered eligible for the systematic review. VR was defined as a fully immersive 3-dimensional computer-generated environment displayed in surround stereoscopic vision on an HMD. Studies that used 360° videos, which are not computer generated, displayed on a VR HMD were considered eligible as well. Studies were included in the meta-analysis if they had at least the following data available: a mean or median score for pain or anxiety during the procedure, as well as a measure of dispersion, for both the intervention and standard care groups. If not available, we requested these data by contacting the authors.

Exclusion criteria were the application of VR in nonsomatic patients samples, audiovisual glasses that offer visual and audio stimulation but do not allow interaction between the user and the computer-generated world, or no distinction made between pediatric and adult patients. Reviews, meta-analyses, single-case studies, dissertations, conference papers, and abstracts were excluded as well.

Search Strategy

An exhaustive search in the following electronic databases was established and conducted by a biomedical information specialist on April 25, 2018 for articles published in English: EMBASE, MEDLINE, CENTRAL, PubMed, Web of Science, and PsycINFO. No date limit was applied to the search. The search terms "VR" and "children" or "adolescents" were used. For each database, different search strategies were developed. Table 1 gives an overview of the search terms that were used.

Data Extraction

A detailed overview of the study selection process is shown in Figure 1. The search yielded 2889 articles. Two of the authors (R.E. and P.F.A.d.N.) first assessed the identified studies for compliance with the inclusion and exclusion criteria, independently. Discrepancies (2%) were discussed until consensus was reached. Based on title and abstract, 44 of the 2889 studies were included. Next, both authors screened the full texts of these articles, independently. Discrepancies (16%) were discussed until consensus was reached. We excluded 27 of the 44 studies. Most of these studies (n = 11) were excluded because they did not use VR. Other reasons included, but were not limited to, overlap with a different age group or no inclusion of pediatric patients (see Figure 1). The final 17 studies were included.

Assessment of Study Quality

Two authors (R.E. and P.F.A.d.N.) independently evaluated the included studies with the Delphi list[23] (Table 2) to evaluate their methodologic quality. The Delphi list is often used in systematic reviews and is able to measure internal validity, external validity, and statistical aspects.[23] The Delphi list contains of 9 items, with equal weights, which can be evaluated as satisfactory (yes: scored 1) or nonsatisfactory (no: scored 0). Discrepancies in scores (17%) were discussed until consensus was reached.

For our assessment, criterion 7 ("Was the patient blinded?") was omitted, as it is impossible to be blinded to wearing a VR HMD or not. Consequently, the maximum possible score for studies in this review was 8 points.

Criteria 5 ("Was the outcome assessor blinded?") and 6 ("Was the care provider blinded?") also concern blinding but were not omitted, as these criteria could be either

Table 1. Literature Search Terms Used for Keywords[a]

No.	Keywords	Included
1	Virtual reality	Virtual reality, virtual reality exposure therapy
2	Children	Boy, child, childhood, girl, infant, kid, pediatrics, preschool, school, toddler
3	Adolescents	Adolescence, adolescent, high school, juvenile, minor, prepubescent, prepuberty, pubescent, puberty, teen, teenager, underaged, youth
	1 AND 2 OR 3	

[a]The following electronic databases were searched: EMBASE, MEDLINE, CENTRAL, PubMed, Web of Science, and PsycINFO.

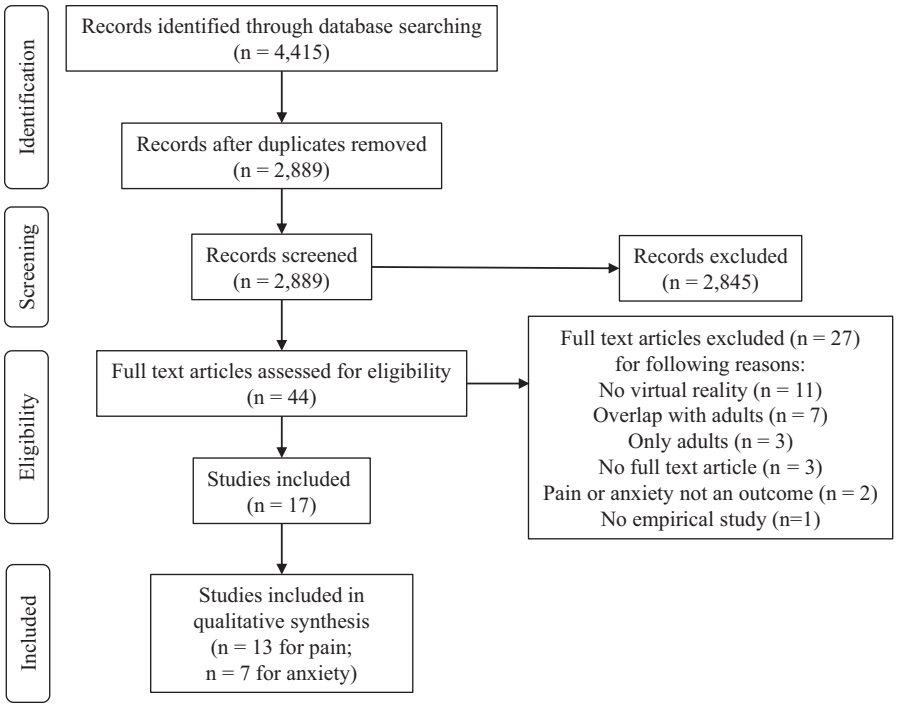

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of study selection.

Table 2. Delphi List for Quality Assessment of Randomized Clinical Trials

Criteria	Evaluation
1. Treatment allocation: Was a method of randomization performed?	Yes (1)/No (0)
2. Treatment allocation: Was the treatment allocation concealed?	Yes (1)/No (0)
3. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes (1)/No (0)
4. Were the eligibility criteria specified?	Yes (1)/No (0)
5. Was the outcome assessor blinded?[a]	Yes (1)/No (0)
6. Was the care provider blinded?[a]	Yes (1)/No (0)
7. Was the patient blinded? [omitted][b]	
8. Were point estimates and measures of variability presented for the primary outcome measures?	Yes (1)/No (0)
9. Did the analyses include an intention-to-treat analysis?	Yes (1)/No (0)

[a]The applicability of criteria 5 and 6 depends on the moment at which virtual reality was applied. When virtual reality was applied before the medical procedure and outcome assessment, the maximum possible score was 8. When virtual reality was applied during the medical procedure and outcome assessment, the maximum possible score was 6.

[b]Criterion 7 was not applicable.

applicable (when VR was applied before the medical procedure and outcome assessment) or nonapplicable (when VR was applied during the medical procedure and outcome assessment).

Synthesis of Results

For the purpose of this systematic review and meta-analysis, we did not include data on distress, maladaptive behavior, nor physiological measures of arousal, such as heart rate. We only included data on pain and anxiety outcomes based on behavioral observations, self-reports, or questionnaires.

Mean scores and SDs for pain and anxiety during the procedure in VR intervention and standard care conditions were either extracted from articles, calculated using median scores and interquartile ranges, or received from authors. Other non–VR intervention conditions were not taken into account in our analyses. Data were entered into a worksheet in Comprehensive Meta-analysis software version 2 (Biostat Inc, Englewood, NJ) by 2 authors (R.E. and B.D.). The following data were also collated and entered into Comprehensive Meta-analysis: first author, publication year, title of study, sample size per condition, mean age per condition, medical procedure, assessment instruments, quality score, informant, and study design. We used patients as primary source of data within each study, because pain and anxiety are subjective experiences. Observations of pain and anxiety made by caregivers and professionals (eg, nurse or researcher) were also entered into the worksheet. Assessment instruments for pain and anxiety were classed as either visual scales (ie, visual analog, graphic rating, and different faces scales) or questionnaires. Study design was divided into parallel or crossover designs. For crossover designs, data from the first period only, that is, before crossover, were included when available. When authors merely provided combined data from both periods, as if groups were parallel, these data were used. When data were available on different components of pain (eg, cognitive, affective, and sensory pain) the sensory component of pain was used in the meta-analysis.

Pain and anxiety were analyzed separately. Effect sizes were generated as standardized mean difference (SMD) by calculating the mean difference on pain or anxiety outcomes between VR and standard care conditions during the procedure and dividing the result by the pooled SD.

Meta-analyses for either pain or anxiety were conducted for overall effect sizes of VR compared to control conditions. Because of the heterogeneity of studies, a random-effects model was used. Sensitivity analyses were performed by removing the study with the largest effect size and studies with low methodological quality (ie, a quality score of 0–2) from both meta-analyses. Separate sensitivity analyses were run for type of medical procedure. Furthermore, we investigated whether informant affected VR effectivity. To achieve a more reliable estimate of effect sizes, we also excluded outlying and low-quality studies from these analyses. To explore if young children respond differently to VR interventions than older children, a meta-regression analysis was performed with mean age of the study samples as predictor and a random-effects model (with methods of moments).

Heterogeneity was assessed using the I^2 statistic, with values ≥75% indicating substantial heterogeneity.[24] In case of substantial heterogeneity, subanalyses were performed to explore sources of heterogeneity. Publication bias was assessed with funnel plot asymmetry and Egger tests.[25] All analyses were performed using Comprehensive Meta-analysis software version 2.

RESULTS

Study Characteristics

Table 3 summarizes the main characteristics and results of the studies. We organized the final 17 studies based on the type of medical procedure. In 16 studies, VR was applied as a distraction technique during dental care (n = 2),[26,27] burn care (n = 6),[28–33] oncological care (n = 4),[34–37] or venous access (n = 4).[38–41] Oncological care includes quite heterogeneous procedures (ie, lumbar puncture),[35] port access (piercing of the skin to access a previously implanted catheter in the chest for chemotherapy),[36,37] or chemotherapy.[34] Only 1 study applied VR preprocedurally, before elective surgery under general anesthesia (n = 1).[42] The studies were conducted between 1999 and 2018. The number of included patients of the studies varied between 7 and 143, with a median of 38.

Fourteen studies were RCTs, of which 10 used a parallel design and 4 studies a crossover design. All RCTs compared the VR intervention group to care as usual (CAU). CAU was often not well defined. However, CAU varied widely and could involve either no distraction or rather intensive distraction, such as watching television or listening to music. Moreover, not all studies made clear whether or not parents remained present during the procedure, nor which pharmacological analgesia were used. Three RCTs added a third condition to their designs: movie distraction,[32] playing a non–VR computer game,[36] or applying external cold and vibration.[40] The 3 non–RCTs trials were quasi-experimental, of which 2 did not use randomization,[26,39] while the other study used an interrupted time series design with removed treatment.[34]

The age range of participants for 16 of the 17 studies varied between 4 and 21 years. One study reported a mean age of 6.5 years but did not indicate the age range.[29] Studies were heterogeneous regarding VR environments (software) and VR hardware.

Study Quality Assessment

We assessed all included studies with the Delphi list[23] to evaluate their methodologic quality. Blinding of the outcome assessor and caregiver (criteria 5 and 6 of the Delphi list) was only applicable to the study of Ryu et al[42] because they applied VR before, instead of during, the medical procedure. Therefore, the maximum possible score for this study was 8, while for the other studies, the maximum possible score was 6 (as the 2 criteria regarding blinding were not applicable).

The included studies varied in quality, as the quality scores ranged between 0 and 6 (see Table 3 for quality scores). The average quality score was 3.5 (SD = 1.7). Most studies had moderate quality, whereas 5 studies had high quality (ie, a maximum score, or 1 point below maximum). Four studies had poor quality (ie, a score of 0–2). Even though in 76% (n = 13) a method of randomization was performed, only 18% (n = 3) of the studies guaranteed a concealed treatment allocation. The majority of studies stated that a randomization scheme or table was used, but not enough information was provided to ensure that the allocation procedure was not transparent before assignment. In more than half of the studies, groups were similar at baseline regarding characteristics such as age, sex, and degree of injury (n = 10, 59%). Inclusion and exclusion criteria were not described precisely enough for 6 studies (35%). Seven studies (41%) included intention-to-treat analysis.

Other specific findings that could have influenced study quality were as follows: initially, Das et al[28] (burn care) only included patients who experienced burns for the first time, but they let some patients participate more than once (ie, 11 trials were undertaken from 7 patients). Piskorz and Czub[39] (venous access) let children play a VR game. If they enjoyed it, these children were included in the VR condition. Afterward, the authors collected data for the control group (who had not tried out the VR game). Gerceker et al[40] excluded all unsuccessful phlebotomy attempts from their analyses (ie, when there was no blood flow into the tube within 5 seconds during the first attempt). Ryu et al[42] observed less anxiety during the preoperative period but did not assess anxiety during induction of anesthesia, when anxiety peaks.

Virtual Reality and Pain Management

As shown in Figure 2, effect sizes for patient-reported pain could be generated for 14 of the 17 studies. For 2 studies, means and SDs were calculated using median values and interquartile ranges.[32,35] Calculated effect sizes were positive when VR reduced pain more than CAU. Across all studies, using a random-effects model, the weighted effect size of VR on pediatric pain during a medical procedure was large (SMD = 1.30; 95% CI, 0.68–1.91; $P < .001$). This indicated a substantial clinical benefit, but heterogeneity of study

Table 3. Characteristics and Results of Included Studies That Report on the Effectiveness of Virtual Reality on Pain and Anxiety in Pediatric Patients Undergoing Medical Procedures (n = 17)

Medical Procedure	Author (Year)	Participants n	Participants Age	Moment of VR	VR Equipment	Treatment Conditions[a]	Study Design	Key Findings	Quality Score[b]
Dental care	Sullivan et al[26] (2000)	30	5–7 y	During restorative treatment	Unknown	VR distraction CAU	Within subjects (not randomized)	No differences in anxiety based on Koppitz human figure drawing test after procedure	0
	Asl Aminabadi et al[27] (2012)	120	4–6 y	During restorative treatment	i-glasses 920HR Ilixco Inc	VR distraction CAU	RCT crossover	Less self-reported pain (faces) and stated anxiety (MCDA [f]) in VR than CAU during procedure	4
Burn care	Das et al[28] (2005)	11[c]	5–16 y	During burn dressing change	IO i-glasses	VR distraction CAU	RCT crossover	Less self-reported pain (faces scale) during procedure in VR than CAU	3
	Chan et al[29] (2007)	8	M = 6.54	During burn dressing change	i-glasses	VR distraction CAU	RCT crossover	No differences in self-reported pain (FPS-r) during and after procedure	1
	Schmitt et al[30] (2011)	54	6–19 y	During postburn physical therapy	nVisor SX VR-1280 ProView XL50 ProView SR80	VR distraction CAU	RCT crossover	Less self-reported cognitive, affective, and sensory pain (GRS) in VR than CAU during procedure	3
	Kipping et al[31] (2012)	41	11–17 y	During burn dressing change	eMagin, Z800 3DVisor	VR distraction CAU (television, stories, or music)	RCT parallel	Less observed pain (FLACC) during procedure in VR than CAU. No differences in self-reported or parent-observed pain (VAS) during procedure	6
	Jeffs et al[32] (2014)	28	10–17 y	During burn treatment	Kaiser Optical SR80a on tripod	VR distraction Non–VR distraction (television) CAU	RCT parallel	Less self-reported pain (APPT-WRGS) during procedure in VR than in non–VR distraction but not less than CAU	5
	Hua et al[33] (2015)	56	4–16 y	During burn dressing change	eMagin Z800 3DVisor	VR distraction CAU (toys, television, books)	RCT parallel	Less self-reported pain (faces) during, less parent-observed pain (VAS) before, during, and after, and less researcher-observed pain (FLACC) during and after procedure in VR than CAU	5
Oncological care	Schneider and Workman[34] (1999)	11	10–17 y	During chemotherapy	Virtual IO	VR distraction CAU	Interrupted time series with removed treatment	No differences in self-reported state anxiety (state-trait anxiety inventory for children-1) during procedure	2
	Sander Wint et al[35] (2002)	30	10–19 y	During lumbar puncture	i-O Display Systems LLC	VR distraction CAU	RCT parallel	No differences in self-reported pain (VAS) during procedure	5
	Gershon et al[36] (2004)	59	7–19 y	During port access for chemotherapy	Unknown	VR distraction Non–VR distraction CAU (personal computer game)	RCT parallel	Less nurse-observed pain (VAS) in VR and non–VR distraction than CAU during procedure No differences in researcher-observed pain (CHEOPS), self-reported or parent-observed pain or anxiety (VAS) during procedure	4
	Wolitzky et al[37] (2005)	20	7–14 y	During port access for chemotherapy	Unknown	VR distraction CAU	RCT parallel	Less researcher-observed pain (CHEOPS) in VR than CAU during procedure No differences in self-reported, parent-observed, or nurse-observed pain or anxiety (VAS) during procedure	4

(*Continued*)

Table 3. Continued

Medical Procedure	Author (Year)	Participants n	Participants Age	Moment of VR	VR Equipment	Treatment Conditions[a]	Study Design	Key Findings	Quality Score[b]
Venous access	Gold et al[38] (2006)	20	8–12 y	During IV placement for magnetic resonance imaging or computed tomography scan	5DT HMD 800 with InterSens InertiaCube2 tracker	VR distraction CAU	RCT parallel	Less self-reported pain (FPS-r) in VR than CAU during procedure No differences in self-reported pain measured with faces during procedure No differences in self-reported, parent-, or nurse-observed pain (VAS) during procedure	5
	Piskorz and Czub[39] (2017)	38	7–17 y	During blood draw	Oculus Rift DK2	VR distraction CAU	Between subjects design (not randomized)	Less self-reported pain (VAS) and anxiety (VAS) than CAU during procedure	1
	Gerceker et al[40] (2018)	121	7–12 y	During blood draw	Samsung Galaxy S5 + Samsung Gear VR	VR distraction External cold and vibration CAU	RCT parallel	Less self-reported, parent-observed, and nurse-observed pain (faces) in both VR and external cold and vibration than CAU during procedure No differences in VR versus external cold and vibration during procedure	3
	Gold and Mahrer[41] (2018)	143	10–21 y	During blood draw	Samsung Galaxy S6 + 1. Google Pixel Merge VR (10–12) 2. Samsung Gear VR (13–21)	VR distraction CAU (television)	RCT parallel	Less self-reported and parent-observed pain (VAS) and anxiety (VAS) in VR than CAU during procedure Patients with high anxiety sensitivity (CASI) benefit more from VR than with low anxiety sensitivity during procedure	3
Preoperative	Ryu et al[42] (2017)	69	4–10 y	Before entering the operating theatre	Samsung Galaxy S6 + Samsung Gear VR	VR exposure CAU (face-to-face information)	RCT parallel	Less researcher-observed preoperative anxiety (m-YPAS) in VR than CAU	5

Manufacturer information for the equipment noted in the table: i-glasses 920HR (Ilixco, Inc, Menlo Park, CA); i-glasses (i-O Display Systems, LLC, Sacramento, CA); nVisor SX (NVIS, Inc, Reston, VA); VR-1280 (Virtual Research Systems, Inc, Aptos, CA); ProView XL50 (Kaiser Electro-Optics, Inc, Carlsbad, CA); ProView SR80 (Kaiser Electro-Optics, Inc, Carlsbad, CA); eMagin Z800 3DVisor (eMagin Corporation, Hopewell Junction, NY); Kaiser Optical SR80a (on tripod; Kaiser Optical Systems, Inc, Ann Arbor, MI); 5DT HMD 800 (5DT, Inc, Irvine, CA); Oculus Rift DK2 (Facebook Technologies, LLC, Menlo Park, CA); Samsung Galaxy S5 (Samsung Electronics Co, Ltd, Suwon, South Korea); Samsung Gear VR (Facebook Technologies, LLC, Menlo Park, CA); Google Pixel (HTC Corporation, New Taipei City, Taiwan); Merge VR (Merge Labs, Inc, San Antonio, TX); Samsung Galaxy S6 (Samsung Electronics Co, Ltd, Suwon, South Korea).

Abbreviations: APPT-WRGS, adolescent pediatric pain tool - word graphic rating scale; CASI, childhood anxiety sensitivity index; CAU, care as usual; CHEOPS, Children's Hospital of Eastern Ontario pain scale; FLACC, face, legs, activity, cry, consolability; FPS-r, faces pain scale-revised; GRS, graphic rating scale; IV, intravenous; M, mean; MCDA (f), modified child dental anxiety scale (f); m-YPAS, modified Yale preoperative anxiety scale; RCT, randomized controlled trial; VAS, visual analog scale; VR, virtual reality.

[a]In all studies, routine pharmacological analgesia was administered, if applicable. Available information on nonpharmacological care as usual (distraction) is stated in brackets.

[b]Maximum possible score for Ryu et al[42] is 8. Maximum possible score for all other studies is 6.

[c]Based on 7 unique subjects, who could participate more than once.

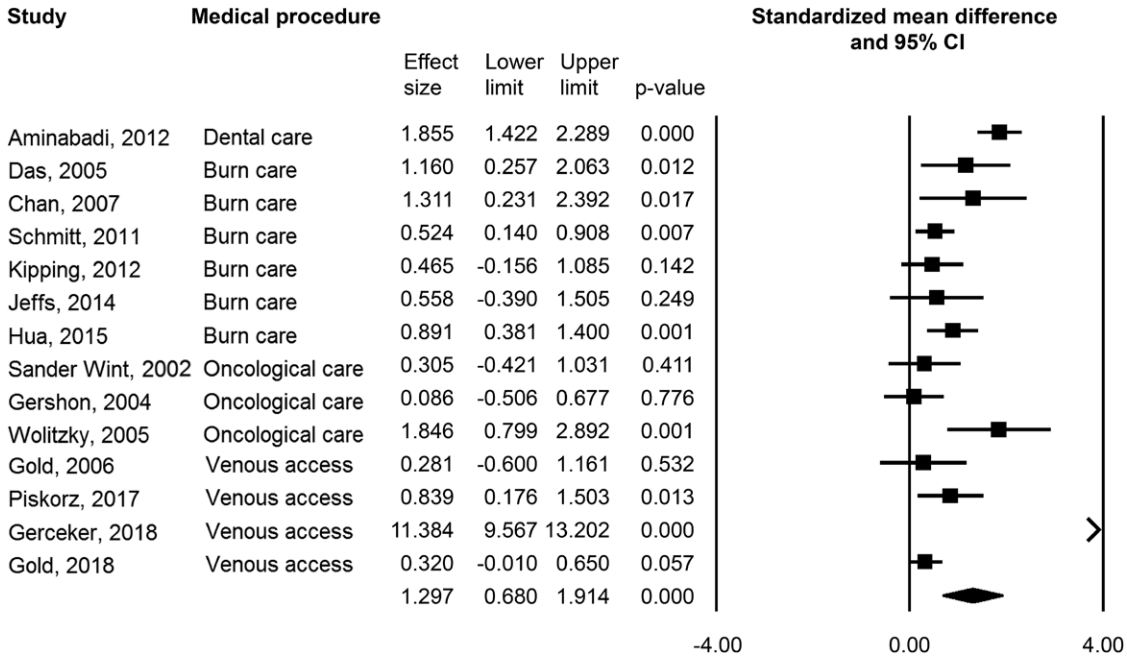

Figure 2. Random-effects meta-analysis for the effect of VR on patient-reported pain during a medical procedure compared to CAU. Note: study effect for Gerceker et al[40] is out of range. CAU indicates care as usual; VR, virtual reality.

effects was high (I^2 = 93.3%). A sensitivity analysis was performed by excluding the outlying study, that is, the study with the largest effect size (Gerceker et al[40]) and studies with low methodological quality.[29,39] This analysis still suggested effects of VR with an attenuated but still medium to large effect size, which indicated a robust effect (SMD = 0.73; 95% CI, 0.35–1.11; P < .001). Though, still substantial, this analysis had lower heterogeneity (I^2 = 78.3%).

The following sensitivity analyses were performed after removal of the outlying study[40] and low-quality studies[29,39] to achieve a more reliable estimate of effect sizes. Sensitivity analyses were run for caregivers and professionals as observers of pediatric pain. We found significant results based on both types of informants (caregivers[31,33,36,41]: SMD = 0.47; 95% CI, 0.22–0.72; P < .001; I^2 = 0.0%, professionals[31,33,36]: SMD = 0.82; 95% CI, 0.48–1.15; P < .001; I^2 = 0.0%). Finally, we ran sensitivity analyses on self-reported pain for each type of medical procedure, when data from >1 study were available. We found significant effects for burn care[28,30–33] (SMD = 0.66; 95% CI, 0.40–0.91; P < .001; I^2 = 0.0%) and venous access[38,41] (SMD = 0.32; 95% CI, 0.01–0.62; P = .046; I^2 = 0.0%) but not for oncological care[35–37] (SMD = 0.65; 95% CI, −0.26 to 1.57; P = .159; I^2 = 76.3%). The suggested effect of VR for observed pain and for self-reported pain during burn care and venous access was associated with decreased effect sizes, but also with zero heterogeneity.

A random-effects model (with methods of moments) was used for the meta-regression analysis with age as a predictor. The results suggested that VR interventions for pain reduction were more efficacious for younger than for older children (P = .015). More specifically, the effect size of VR on pain decreased with 0.26 when age increased with 1 year. After removing the study with the largest effect size,[40] age was still a significant predictor of the effect of VR on pain (P < .001).

Virtual Reality and Anxiety Management

Effect sizes for patient-reported anxiety could be generated for 7 of the 17 studies (Figure 3). For 1 study, mean and SD were calculated using median value and interquartile range.[42] Using the random-effects model, a large effect size was found for VR on anxiety (SMD = 1.32; 95% CI, 0.21–2.44; P = .020). This indicated substantial clinical benefit, but heterogeneity of study effects was high (I^2 = 96.6%). A sensitivity analysis was performed by excluding the outlying study (Asl Aminabadi et al[27]) and studies with low methodological quality.[34,39] This analysis still suggested effects of VR (SMD = 0.50; 95% CI, 0.20–0.79; P = .001) with an attenuated but still medium effect size, which indicated a robust effect. Moreover, heterogeneity decreased significantly in this analysis (I^2 = 22.4%).

The following sensitivity analyses were performed after removal of the outlying study[27] and low-quality studies[34,39] to achieve a more reliable estimate of effect sizes. Unfortunately, very limited data were available for caregivers and professionals as observers of pediatric anxiety. We were only able to run a separate analysis for caregiver as informant,[36,41] which did not yield a significant result (SMD = 0.31; 95% CI, −0.02 to 0.63; P = .067; I^2 = 0%). Regarding different types of medical procedures, only for oncological care, enough data were available to run a sensitivity analysis on self-reported anxiety,[36,37] which yielded a significant result (SMD = 0.53; 95% CI, 0.10–0.96; P = .015; I^2 = 0.0%). The effect of VR during oncological care was associated with a decreased effect size but also with zero heterogeneity.

A random-effects model (with methods of moments) was used for the meta-regression analysis with age as a predictor. The results suggested that VR interventions for anxiety reduction were more efficacious for younger than for older children (P = .023). More specifically, the effect size of VR on anxiety decreased to 0.35 when age increased with 1 year. After

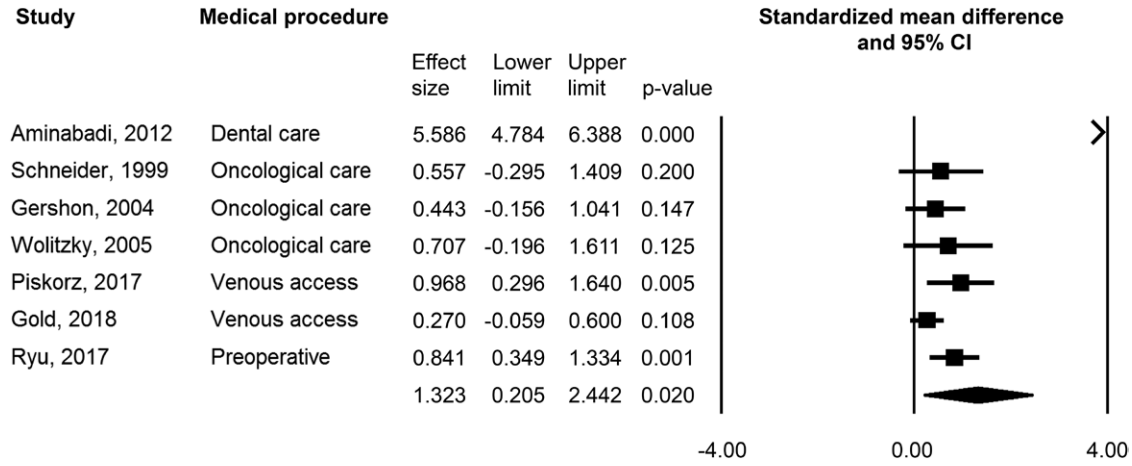

Figure 3. Random-effects meta-analysis for the effect of VR on patient-reported anxiety during a medical procedure compared to CAU. Note: study effect for Asl Aminabadi et al[27] is out of range. CAU indicates care as usual; VR, virtual reality.

removing the study with the largest effect size,[27] age was still a significant predictor of the effect of VR on anxiety ($P = .037$).

Publication Bias and Heterogeneity

Funnel plots for pain and anxiety showed asymmetry, but Egger regression asymmetry tests did not confirm the presence of a significant publication bias for pain ($P = .105$) nor anxiety ($P = .282$). Funnel plots indicated that there was one clear outlier for pain[40] and one for anxiety.[27] These outliers correspond to the studies with the largest effect sizes which we have removed from the sensitivity analyses.

As discussed above, substantial heterogeneity of study effects was found for the overall meta-analysis on pain ($I^2 = 93.3\%$) and anxiety ($I^2 = 96.0\%$). We found that the outlying and low-quality studies were important sources of heterogeneity, because removal of these studies was associated with decreased heterogeneity ($I^2 = 78.3\%$ for pain and $I^2 = 22.4\%$ for anxiety). Moreover, the available data suggested that the different medical procedures were an important source of heterogeneity as well because the study effects of these sensitivity analyses were associated with zero heterogeneity.

DISCUSSION

This is the first systematic review and meta-analysis that specifically focused on VR in pediatric patients. Our meta-analysis, based on 14 studies for pain and 7 studies for anxiety, showed VR to be an effective tool to diminish patient-reported pain (SMD = 1.30) and anxiety (SMD = 1.32) during a range of medical procedures. The effect of VR on pediatric pain was also significant when observed by caregivers or professionals. For anxiety, limited observer data were available on VR effectivity. Due to small groups, it was difficult to compare VR effectivity in different types of medical procedures. VR was most often applied during burn care.

Our results showed that VR interventions for pain and anxiety were potentially more efficacious for younger than for older children. A possible explanation is that younger children tend to have higher levels of anxiety before medical procedures.[43,44] A different possible explanation is that VR is especially engaging for younger children, as they are often more engaged in magical thinking[45] and become truly captivated by imaginative play.[15]

However, because the relationship of age with VR efficacy on pain or anxiety could be different within each study compared to across studies, the relationship shown between age and VR efficacy in the meta-regression may not represent the true relation. This phenomenon is called ecological fallacy.[46]

VR was found to be significantly more effective in reducing pain and anxiety than CAU. However, it remains difficult to differentiate between the added value of VR over other forms of distraction, for example, watching television, and no distraction, because CAU was often not well defined. The high weighted effect sizes we found suggest that VR distraction is possibly more effective than other distraction interventions during medical procedures. For example, a Cochrane review[47] found an effect size of 0.61 for the impact of distraction (eg, games, music, and toys) on self-reported pain during needle-related procedures. Similarly, a meta-analysis including trials on music therapy as distraction during different types of medical procedures (eg, dental care, magnetic resonance imaging scans, and venipuncture) showed a significant reduction in pain and anxiety with an effect size of 0.35.[48] Because VR exposure as a preparation tool for medical procedures is a fairly unexplored area of research, it is not (yet) possible to compare effect sizes for VR preparation to other forms of preparative interventions to reduce pain and anxiety during medical procedures.

The studies in the current systematic review and meta-analysis varied in quality. Most studies applied randomization and clearly described their inclusion and exclusion criteria. However, concealed treatment allocation was often not guaranteed and intention-to-treat analyses were often not performed. Also, very few studies focused on possible moderating factors of VR effectivity, such as anxiety sensitivity and temperament.

An important area of focus is immersion, which is influenced by interaction with the virtual environment by means of translation (changing position), rotation (changing orientation), point of view (perspective), and field of view.[19,49] Non–VR content, that is, regular (cartoon) videos or 360° videos, creates less immersion, because the user

is limited to the filmmaker's movements and progress of the video. This difference in content is important, as it has been hypothesized that more immersion is related to more pain reduction, because less attention is available for pain perception.[13,14] Even though some studies included questions about subjective feelings of immersion, it is difficult to objectively analyze this phenomenon. During certain medical procedures, for example, dental treatment, patients were required to keep their head still, which may have limited immersion as well. True VR creates a more compelling illusion of presence in the virtual world than more passive audiovisual glasses and non–VR (360°) videos. However, the supposed superiority of VR over audiovisual glasses and non–VR content regarding efficacy in medical care has yet to be proven.[11] Therefore, the role of immersion should be a focus of future research.

Implications

VR distraction has a large impact on pediatric pain and anxiety during medical procedures, especially for younger children. This easy-to-use tool can be used effectively in clinical practice. More research like the study of Ryu et al[42] is needed to establish evidence on VR exposure as preparation to reduce pain and anxiety during medical procedures. This is crucial, because anticipatory anxiety can lead to more pain and distress during the medical procedure itself.[50,51]

Limitations

The following limitations should be taken into account when interpreting the results of the current review and meta-analysis. First, effect sizes for patient-reported anxiety could be generated for only 7 studies. Second, limited observer data were available, especially for anxiety outcomes. Third, means and SDs were estimated using median values and interquartile ranges for 3 studies.[32,35,42] This was necessary to pool all data, but is unclear how reliable these estimations are. Fourth, substantial heterogeneity was present in the findings. We have identified outlying and low-quality studies as important sources of heterogeneity. Moreover, there was a difference in effect of VR for different medical procedures, so one should be careful when generalizing the suggested effect for VR to clinical practice. However, in our opinion, the mean pooled effect of all medical procedures still provides the most useful information, especially because certain procedures have not been studied extensively or have not been studied at all, regarding VR interventions. Finally, the included studies applied various kinds of VR software, which could have influenced the amount of immersion and VR effectivity. On the other hand, it is also possible that VR software only plays a small role, as Kenney and Milling[21] found no differences in their meta-analysis between commercially available VR games and VR software that was specifically developed for distraction.

CONCLUSIONS

This systematic review and meta-analysis indicate that pediatric patients undergoing a range of medical procedures benefit from VR as a tool to reduce pain and anxiety. Due to limited available observer data, we could not provide insight into possible differences in perspective between patients, caregivers, and professionals. VR research in pediatrics has mainly focused on VR as a distraction tool. Using VR exposure as a preparation tool could be an innovative way to decrease anxiety and pain before and during medical procedures. However, further research into this field is needed.

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