



SYSTEMATIC REVIEW & META-ANALYSIS

The effect of virtual reality on procedural pain and anticipatory anxiety in children admitted to emergency room: systematic review and meta-analysis

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Findings:

Virtual reality interventions appear to have a positive significant influence on pain and anxiety in children admitted to emergency rooms.

ABSTRACT

BACKGROUND: Virtual reality (VR) is a recent distraction technique used for pain management in pediatric settings. None of the reviews available in the literature addresses the effectiveness of intervention in the emergency room, which is known to be an environment at risk of generating great stress for both children and caregivers.

OBJECTIVE: To measure the effect of VR on procedural pain and anticipatory anxiety in children admitted to the emergency room.

METHODS: Systematic review with meta-analysis of parallel-group randomized controlled trials (RCTs). Sources of query, consultation, and retrieval were as follows: biomedical databases, online resources, and registries of RCTs. VR was compared with usual care. The primary outcome was procedural pain; the secondary outcome was anticipatory anxiety. The RoB 2 tool was used to assess the risk of bias. The point estimate of intervention effect was measured by standardized mean difference (SMD) while certainty/quality of outcome was presented by the GRADE approach.

RESULTS: Six RCTs with 443 subjects and variable risk of bias were included. VR demonstrated a small but statistically significant benefit on both procedural pain (SMD: -0.32, 95% CI: -0.56, -0.09; N=409) and anticipatory anxiety (SMD: -0.26, 95% CI: -0.45, -0.06; N=409).

CONCLUSION: Children admitted to the emergency room who underwent the intervention had a small but significant reduction in procedural pain and anticipatory anxiety; however, further studies with a larger sample sizes and better methodological quality are needed to confirm the findings.

KEYWORDS: *Virtual Reality, Procedural Pain, Anticipatory Anxiety, Children, Emergency Room*

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REVISIONE SISTEMATICA & META-ANALISI

L'effetto della realtà virtuale sul dolore procedurale e sull'ansia anticipatoria nei bambini ricoverati al pronto soccorso: revisione sistematica e meta-analisi.

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Riscontri:

Interventi di realtà virtuale sembrerebbero influire con positiva significatività su dolore e ansia nei bambini ricoverati in pronto soccorso.

ABSTRACT

BACKGROUND: La realtà virtuale (VR) è una recente tecnica di distrazione utilizzata per la gestione del dolore in ambito pediatrico. Nessuna delle revisioni disponibili in letteratura affronta l'efficacia di un intervento simile in pronto soccorso, che notoriamente è un ambiente a rischio di generare grande stress sia per i bambini che per gli operatori.

OBIETTIVO: misurare l'effetto della VR sul dolore procedurale e sull'ansia anticipatoria nei bambini ricoverati in pronto soccorso.

METODI: revisione sistematica con meta-analisi di studi randomizzati controllati a gruppi paralleli (RCT). Le fonti di interrogazione, consultazione e reperimento sono state le seguenti: banche dati biomediche, risorse online e registri di RCT. La VR è stata confrontata con le cure abituali. L'esito primario era il dolore procedurale, l'esito secondario l'ansia anticipatoria. Lo strumento RoB 2 è stato utilizzato per valutare il rischio di bias. La stima puntuale dell'effetto dell'intervento è stata misurata mediante la differenza media standardizzata (SMD), mentre la certezza/qualità dell'esito è stata presentata mediante l'approccio GRADE.

RISULTATI: sono stati inclusi sei RCT con 443 soggetti e rischio di bias variabile. La VR ha dimostrato un beneficio piccolo ma statisticamente significativo sia sul dolore procedurale (SMD: -0,32, 95% CI: -0,56, -0,09; N=409) sia sull'ansia anticipatoria (SMD: -0,26, 95% CI: -0,45, -0,06; N=409).

CONCLUSIONE: i bambini ricoverati al pronto soccorso che hanno subito l'intervento hanno avuto una piccola ma significativa riduzione del dolore procedurale e dell'ansia anticipatoria; tuttavia, per confermare i risultati sono necessari ulteriori studi con campioni più ampi e una migliore qualità metodologica.

KEYWORDS: *Realtà virtuale, Dolore, Ansia anticipatoria, Bambini, Pronto soccorso*

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BACKGROUND

The recommended approach for the management of procedural pain in pediatric settings should include both pharmacological and non-pharmacological interventions [1-3], with the latter being the starting point [4] because they are relatively risk-free, low-cost and easy to administer and safer and more effective in relieving pain and anxiety [5]. Among the most widely used non-pharmacological interventions are distraction techniques [6]. To more pervasively capture a child's attention and thus achieve maximum effectiveness, distraction should be multisensory, immersive, neurodevelopmentally appropriate, and highly engaging [7,8].

One of the techniques that has become increasingly popular in clinical settings in recent years is virtual reality (VR). It has been defined as a computer technology that creates a simulated world that subjects perceive as comparable in terms of objects or events to the real one [9]. Through VR, attention is diverted away from real-world stimuli and into the virtual world through the multisensory nature of the virtual environment [10]. This is presented in real-time through computer-generated 3D graphics; the individual interacts with virtuality through input devices such as position trackers, mouse or interactive glove, and output devices such as goggles, viewers equipped with motion detectors, sound-producing headphones for reproducing audio stimuli and haptic sensors [11]. Depending on the equipment used, the content and nature of the virtual world, and the level of engagement, VR interventions can be very different [11], although active interaction, navigation, and immersion are recognized as key features [12,13]. Although the mechanism by which VR influences the perception of pain remains unclear, it is believed that this occurs through its ability to attract the child's attention [14]: by focusing at a sensory, cognitive, affective, and behavioral level on the virtual environment with which he or she is interacting, he or she reacts more slowly to pain signals because he

or she is overpowered by pleasant stimuli [15]. The effect appears to be positively associated with an increased degree of immersion [16], probably due to an incremental overregulation of non-painful neural signaling [17], which is counterbalanced by a progressive suppression of nociceptive processing [18,19].

The focus on VR as a distraction technique for pain and anxiety control is going hand in hand with the increasing popularity of the intervention in pediatric settings and is also evidenced by the presence of several dedicated systematic reviews in the literature [7,20-26]. However, none of them focus on the effectiveness of intervention in the emergency room, a setting that, for children and caregivers, is a source of great stress due to the hustle and bustle of health workers, loud sounds, bright lights, and long waiting times, and because young patients may be subjected to medical procedures that generate pain, anxiety, and discomfort [6,27].

Objective

To measure the effect of VR on procedural pain and anticipatory anxiety in children admitted to the emergency room.

METHODS

Inclusion criteria

The inclusion criteria were as follows: (1) participants: subjects aged 0-18 years undergoing medical procedures for diagnostic or therapeutic purposes in the emergency room; (2) intervention: VR; (3) control: Standard of care (SoC); (4) outcomes (assessed with any type of instrument): (a) primary outcome – procedural pain reported by the child after the procedure; (b) secondary outcomes – anticipatory anxiety reported by the child after the procedure, child's pain perceived by the caregiver after the procedure, child's anxiety perceived by the caregiver



after the procedure; (5) study design: parallel-group randomised controlled clinical trials.

Search strategy

The review protocol was registered in PROSPERO (ID: CRD42022312823). The document search was performed on 22 July 2022 and updated on 13 December 2022. The biomedical databases The Cochrane Library, MEDLINE (via PubMed), EMBASE (via Elsevier), CINAHL (via EBSCOhost), PsycINFO (via Ovid), Web of Science (via Clarivate Analytics), Scopus (via Elsevier), ERIC (via Proquest), LILACS (via Virtual Medical Library), CNKI and SciELO were queried. The following keywords with their synonyms were used: "virtual reality," "pain," and "emergency room." The keyword "anxiety" was also not implemented to make the search more sensitive. The search strategy (e.g., MEDLINE) is shown in *Appendix 1*.

The resources ProQuest Dissertations & Theses Global, TRIP Medical Database, the websites Google Scholar, Grey Guide, Grey Literature Report, Grey Literature in the Health Sciences, and the trial registries ICTRP, ClinicalTrials.gov, EU Clinical Trials Register, and ISRCTN registry were also consulted. A manual search was performed on journals that published eligible studies and those relevant to the topic, such as Virtual Reality, The International Journal of Virtual Reality, International Journal of Virtual and Augmented Reality, International Journal of Virtual Technology, and Multimedia. References of both eligible studies and those of relevant systematic reviews were analyzed. Finally, the corresponding authors of the eligible studies were contacted by e-mail to find out whether they had recently completed or were currently conducting other studies of interest. No language or publication date limits were imposed.

Study selection and data extraction

The authors (LGR and VF) independently consulted the sources of information, selected records by title and abstract, or analyzed the full document in doubtful cases. Comparison and discussion were the basis for resolving any disagreements. The authors themselves independently and using a standardized template extracted these data from each eligible study: first author, year of publication and country; study design; type of procedure performed; sample characteristics (total and per-group numerosity, mean or median total and per-group age, percentage of males); exclusion criteria; intervention characteristics and VR scenario; control characteristics; outcome of interest and evaluation tools; mean or median duration of the procedure in minutes.

Risk of bias

Independently, the authors (LGR, VF, SC) assessed the risk of bias with the Risk of Bias 2 (RoB 2) tool [28]. Any disagreement was resolved through comparison and discussion; if a difference of opinion remained, the diriment opinion of another author (LZ) was sought.

Data analysis and synthesis

Estimation of the overall mean effect of the intervention was calculated by creating meta-analyses with a random-effects model and producing forest plots in the presence of at least two studies per outcome. The standardized mean difference (SMD) for continuous measures was operationalized using Cohen's d; as a function of d values of 0.2, 0.5, and 0.8 [29], the effect was assumed to be minor, moderate, or large, respectively. For the calculate the deviation from the point estimate of the effect in each study and from the overall estimate in the aggregated studies, a 95% confidence interval was considered. With Cochran's Q test [30], the presence of heterogeneity among studies was assessed, while its quantification was performed with the

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implementation of Higgins' I^2 index [31]. A low, moderate, high, or very high level of heterogeneity was assigned to I^2 values $\leq 30\%$, 30-60%, 60-90%, or $> 90\%$, respectively [32]. Data processing was performed with ProMeta© version 3.0 software.

Sensitivity analysis

Sensitivity analysis was performed by regenerating the meta-analysis after the exclusion of studies (a) with a high risk of bias and (b) that claimed to have received funding or donations and with at least one author with conflicts of interest.

Additional analysis

Subgroup analyses were performed to assess the effectiveness of the intervention according to the gender and age of the participants.

Publication bias

The funnel plot [33] was inspected, and the Trim and Fill [34] method was implemented to assess the risk of bias, provided at least five studies were available. An objective type assessment was also performed through Egger's test [35] and Begg and Mazumdar's test [36]. The study adheres to PRISMA guidelines [37] in terms of conduct and presentation.

Summary of findings.

The overall assessment of the certainty/quality of evidence was carried out using the GRADE approach [38] by the authors (LGR, VF) independently of each other. Comparison and discussion guided the handling of any disagreements; however, if a difference of opinion persisted, arbitration by another author (LZ) was requested.

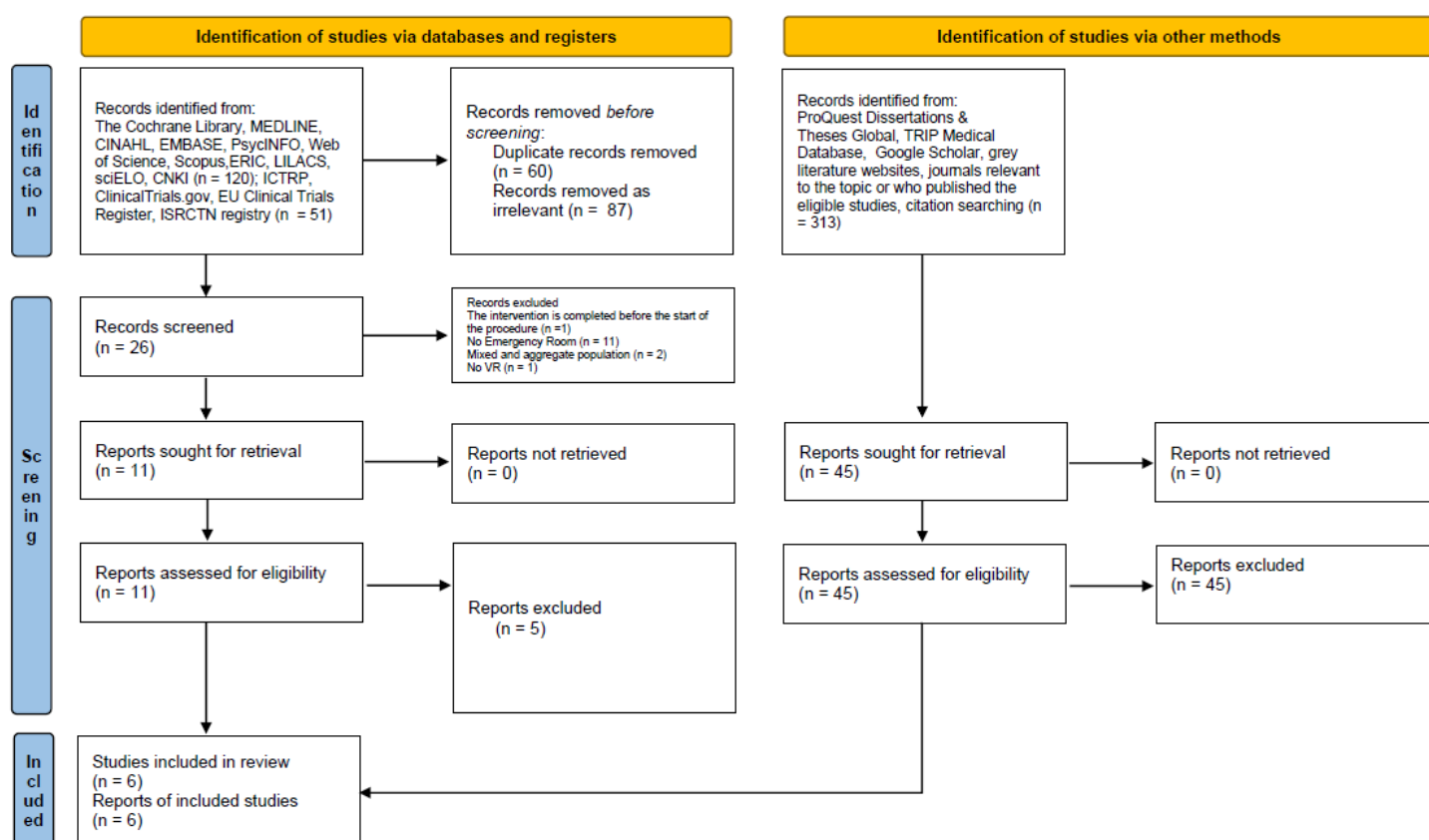


Figure 1: PRISMA flow chart for records screening.

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RESULTS

Selection of studies

As a result of consulting information sources, 484 records were returned; *Figure 1* shows the selection flow of identified records.

No other studies of interest were intercepted through analysis of bibliographies of eligible studies and previous systematic reviews and by consulting the most relevant journals in the field, as well as by

contacting the corresponding authors of eligible studies by e-mail. Of the 11 eligible studies, three were excluded because they did not have a measurement of pain after the procedure but only the pre-post difference [39-41], one because the authors implemented a different intervention than the one of interest [42], and another because it was a quasi-randomized clinical trial [43]. A total of six studies met all the expected inclusion criteria [44-49].

Study (year)	Design	Country	Procedure	Sample	Exclusion criteria	Intervention (VR scenario)	Control	Outcome and evaluation tools	Average procedure duration
Chen (2020)	RCT	Taiwan	Venous sampling, intravenous cannulation	N=136 mean age: 9.3 years VR group (n=68) Nine years control group (n=68) males 56.6%	Children with developmental delay, epilepsy, or heart disease; undergoing chemotherapy; with vision or hearing impairment; nearsighted with more than eight diopters or farsighted with more than five diopters; who have suffered a head injury in the last month; obese; in need of blood transfusions; who have received two or more injections, who have had the procedure performed once before	Interactive, immersive VR (roller coaster, space exploration, nature park, travel destinations)	Verbal comfort	Pain: WBFPs Fear: CFS	VR group: 0.9 minutes Control group: 1 minute
Dumoulin (2019)	RCT	Canada	Venous sampling, intravenous cannulation,	N=59 mean age: 13.9 years VR group (n=20) 12.7 years minimal distraction group (n=24) 13.8 years control group (n=15); males 64.4%	Children with cognitive impairment, who suffer from epilepsy or migraine, who have vomiting at the time of the procedure	Immersive interactive VR (exploring an apartment by hitting flies flying around)	Minimal distraction: portable DVD player (Looney Tunes, Animal Planet's Funniest Animals) Control: CLS prompting the child to choose between a conversation on a topic of choice, books with puzzles, ball of 20 quiz questions	Pain: VAS Fear: VAS	Not declared
Goldman (2021a)	RCT	Canada	Venous sampling, intravenous cannulation	N=66 median age: 8.9 years VR group (n=35) 9.6 years control group (n=31) males 54.5%	Children in poor clinical condition or such that they are excluded from being able to describe pain or anxiety, with facial trauma at the point where the garrisons are to be placed	Interactive, immersive VR (Roller Coaster)	Distraction techniques of your choice (e.g., books, DVD movies, TV, iPad, bubbles) + CLS	Pain: FPS-R Anxiety: VSA	VR group: 5 minutes Control group: 7 minutes
Goldman (2021b)	RCT	Canada	Wound care	N=62 median age: 9.8 years VR Group (n=32) 10.4 years control group (n=30) males 62.9%	Children with wounds or injuries to the face in the area to be covered with the principals	Interactive, immersive VR (Roller Coaster)	Distraction techniques of your choice (e.g., books, DVD movies, TV, iPad, bubbles) + CLS	Pain: FPS-R Anxiety: VSA	VR group: 15 minutes. Control group: 27.4 minutes
Litwin (2021)	RCT	Canada	Venous sampling, intravenous cannulation	N=58 mean age: 12.5 years VR Group (n=31) 12.48 years control group (n=27) males 56.9%	Children with visual, hearing, or cognitive impairment, psychiatric conditions, infections, or injuries to the skin, face, ears, upper limbs	Interactive, immersive VR (kindVR Aqua)	Tablet with marine setting video + soundproof headphones + CLS	Pain: NRS Anxiety: CFS	VR group: 4 minutes Control group: 4.1 minutes
Osmanliu (2021)	RCT	Canada	Venous sampling, intravenous cannulation	N=62 mean age: 11.1 years VR Group (n=31) 12.3 years control group (n=31); males 38.7%	Unstable child or urgent procedure; significant cognitive impairment; diagnosis of epilepsy or seizures; caregiver unavailable	Interactive, immersive VR (Dreamland) + caregiver comfort	Distraction techniques provided by caregiver or CLS + caregiver comfort	Pain: NRS Anxiety: CFS	Not declared

CFS=Children's Fear Scale; CLS=Child Life Specialist; FPS-R=Faces Pain Scale-Revised; NRS=Numerical Rating Scale; RCT=Randomized Controlled Trial; VAS=Visual Analogue Scale; VR=Virtual Reality; VSA=Venham Situational Anxiety; WBFPs=Wong Baker Faces Pain Scale.

Table 1: main characteristics of included studies.



The main characteristics of the included studies

The studies were published between 2019 and 2021, conducted in Canada [45-49] and Taiwan [44], and all in the emergency room of a tertiary care hospital (Table I). Three studies [45,48,49] received some form of funding or donation, and at least one of their authors declared conflicts of interest. A total of 443 children (55.8% male) with a mean age range of 8.9-13.9 years were included. The sample size ranged from 58 [48] to 136 [44] individuals. With the exception of one study, in which the medical procedure consisted of wound care [47], in the others the procedures were venous sampling or intravenous cannulation. Exclusion criteria included children with cognitive impairment, epilepsy, limited communication skills, impaired vision, and hearing, or injuries/infections to the upper limbs, face, ears, and head; clinically critical or hemodynamically unstable children were also excluded. When reported, topical anesthetic administration involved up to 96.8% of children [47]. VR scenarios were heterogeneous, although the most common was Roller Coaster [44,46,47]. In one study, the intervention was combined with caregiver comfort [49]. The control group received Standard of care (SoC), which could range from verbal comfort [44] to the use of a tablet with soundproof headphones and support from a Child Life Specialist (CLS) [48]. One study [45] planned two control groups, one with minimal

distraction (portable DVD player; n = 24) and one with SoC (distraction techniques agreed upon with the CLS; n = 15). All studies assessed pain and anxiety (or fear) reported by the child; one study measured the child's pain as perceived by the caregiver [44], one measured the child's distress [48], and another measured the child's distress as perceived by the caregiver [49]. The instruments used to measure pain included the FPS-R (Faces Pain Scale-Revised) [50], the NRS (Numerical Ratings Scale), the VAS (Visual Analogue Scale), and the WBFPS (Wong-Baker Faces Pain Scale) [51]. Anxiety (or fear) was assessed with the Children Fear Scale (CFS) [52], the VAS, and the Venham Situational Anxiety (VSA) scale [53]. The average duration range of the procedure in the intervention group was 0.9-15 minutes, and in the control group, 1-27.4 minutes. The studies also assessed other outcomes, such as the number of attempts required for successful venous sampling or intravenous cannulation, the level of satisfaction with the intervention of children and caregivers, the degree of acceptability of physicians and other caregivers, and possible side effects.

Risk of bias

Figure 2 and Figure 3 show the risk of bias assessment of the included studies. Overall, the risk of bias is high for four studies [44,45,48,49] and of some concern for two [46,47].

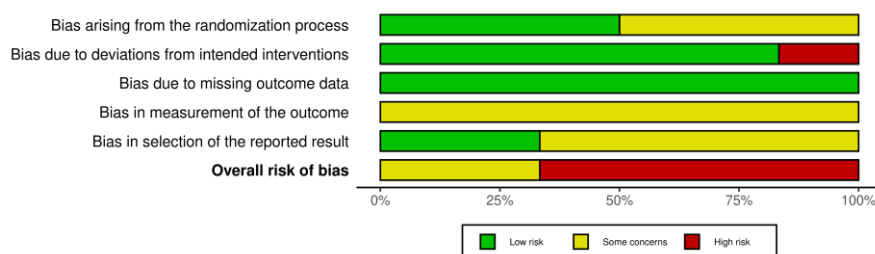


Figure 2: RoB2 summary

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Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Chen 2020	-	+	+	-	-	×
Dumoulin 2019	-	+	+	-	-	×
Goldman 1 2021	+	+	+	-	+	-
Goldman 2 2021	+	+	+	-	+	-
Litwin 2021	-	+	+	-	-	×
Osmanlliu 2021	+	×	+	-	-	×

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 × High
 - Some concerns
 + Low

Figure 3 – RoB 2 traffic light

Data analysis

Two studies [46,49] illustrated the results using medians and interquartile ranges or ranges; a conversion technique was implemented to obtain mean and standard deviation [54,55].

Pain – virtual reality vs. Standard of care

The effect of VR vs. SoC for procedural pain in

children undergoing medical procedures in the emergency room were evaluated in 409 participants. The aggregate SMD is -0.32 (95% CI: -0.56, -0.09) in favor of the intervention; the result is statistically significant (Table 2 & Figure 4). The Q-test shows non-significant ($p = 0.247$) and low grade of heterogeneity ($I^2 = 24.88\%$).

Study	Virtual Reality			Standard of care			Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Chen (2020)	3.35	2.38	68	4.35	2.95	68	27.62%	-0.37 [-0.71, -0.03]
Dumoulin (2019)	21.75	20.92	20	25.33	25.25	15	10.17%	-0.16 [-0.83, 0.51]
Goldman (2021a)	2	3.09	35	4	3.11	31	16.53%	-0.65 [-1.14, -0.15]
Goldman (2021b)	1.84	1.94	32	1.47	2.03	30	16.36%	0.19 [-0.31, 0.69]
Litwin (2021)	2.6	2.1	24	3.8	2.1	24	13.04%	-0.57 [-1.15, 0.01]
Osmanlliu (2021)	3.36	3.89	31	3	3.11	31	16.27%	-0.33 [-0.83, 0.17]
Total (95% CI)			210			199	100.00%	-0.32 [-0.56, -0.09]

Heterogeneity statistics: $Q = 6.66$ ($p = 0.247$); $I^2 = 24.88$; $T^2 = 0.02$; $T = 0.14$

Table 2: children's Pain in Emergency Room: virtual reality vs. Standard of care

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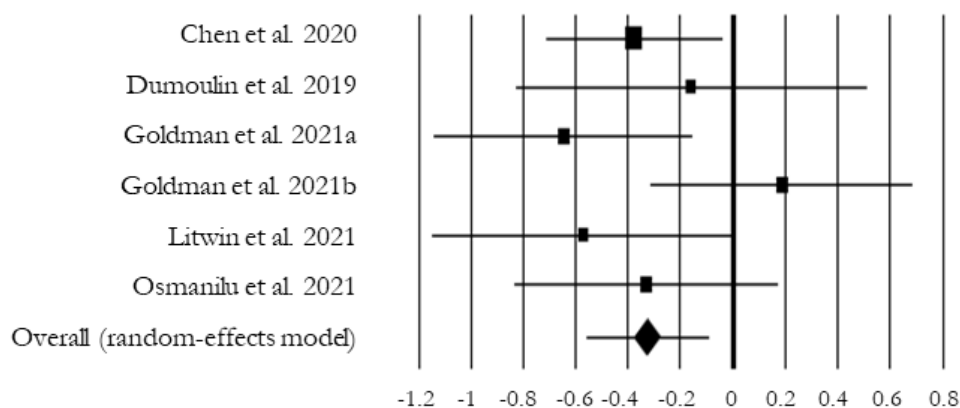


Figure 4: Std. Mean Difference IV, Random, 95% CI

Anxiety/fear – virtual reality vs. Standard of care

The effect of VR vs. SoC on the anxiety/fear of children undergoing medical procedures in the emergency room was evaluated in 409 participants. The aggregate

SMD is -0.26 (95% CI: -0.45, -0.06) in favor of the intervention; the result is statistically significant (Table 3 & Figure 5). The Q-test shows no heterogeneity ($p = 0.430$), and the Higgins index is zero.

Study	Virtual Reality			Standard of care			Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Chen 2020	3.35	2.38	68	4.35	2.95	68	33.46%	-0.35 [-0.69 -0.02]
Dumoulin 2019	21.75	20.92	20	25.33	25.25	15	8.44%	-0.35 [-1.02, 0.33]
Goldman 2021a	2	3.09	35	4	3.11	31	16.43%	0.00 [-0.48, 0.48]
Goldman 2021b	1.84	1.94	32	1.47	2.03	30	15.47%	-0.04 [-0.54, 0.46]
Litwin 2021	2.6	2.1	24	3.8	2.1	24	11.49%	-0.08 [-0.66, 0.50]
Osmanliu 2021	3.36	3.89	31	3	3.11	31	14.71%	-0.65 [-1.16, -0.14]
Total (95% CI)			210			199	100.00%	-0.26 [-0.45, -0.06]

Heterogeneity statistics: $Q = 4.89$ ($p = 0.430$); $I^2 = 0.00$; $T^2 = 0.00$; $T = 0.00$

Table 3: children's anxiety/fear in the emergency room: virtual reality vs. Standard of care.

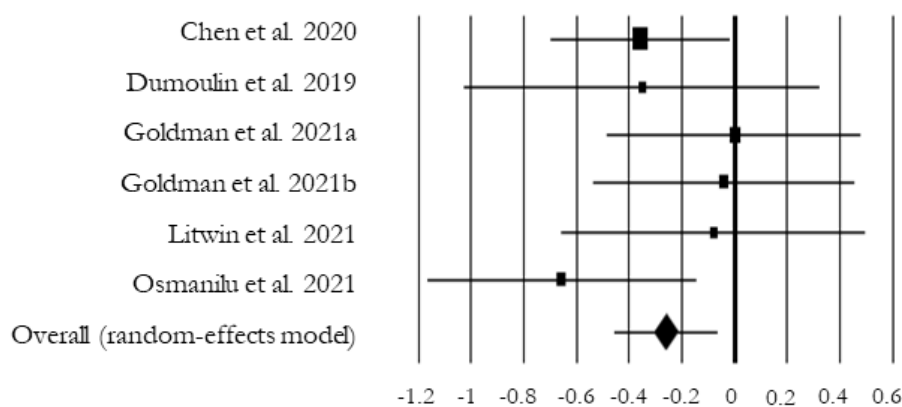


Figure 5: std. Mean difference IV, random, 95% CI

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Child pain as perceived by caregiver – virtual reality vs. Standard of care

Only one study [44] evaluated the effect of VR versus SoC on child pain as perceived by the caregiver, so no meta-analysis was performed.

Child's anxiety/fear as perceived by caregiver – virtual reality vs. Standard of care

No studies evaluated the effect of VR versus SoC on anxiety or fear of the child as perceived by the caregiver.

Other outcomes

The studies that measured the average duration of the procedure and/or the number of attempts required for successful venous sampling or intravenous cannulation always recorded lower values in the VR group; furthermore, the level of satisfaction with the intervention of children and caregivers and the degree of acceptability of doctors and other caregivers was more than satisfactory. The side effects observed were mild and occasional (eye fatigue, nausea, dizziness, headache).

Sensitivity analysis

To assess the robustness of the overall effect of the intervention on pain, the meta-analysis was regenerated after the removal of studies (a) at high risk of bias [44,45,48,49]; (b) that received funding or donations and with one or more authors declaring conflicts of interest [45,48,49]. The aggregate SMD after the removal of studies with a high risk of bias is -0.23 (95% CI: -1.05, 0.59; N = 128) in favor of intervention; the result is not statistically significant. The Q-test shows a significant ($p = 0.020$) and high degree of heterogeneity ($I^2 = 81.38\%$). After removing studies with conflicts of interest and funding or donations, the aggregate SMD was -0.29 (95% CI: -0.72, 0.14; N = 264) in favor of the intervention; the result is not statistically significant. The Q-test shows heterogeneity at the limit of

significance ($p = 0.058$) and to a moderate degree ($I^2 = 64.84\%$).

Additional analysis

Gender

No studies have evaluated the effect of the intervention according to the gender of the participants.

Age

No studies assessed the effect of the intervention as a function of the age of the participants.

Publication bias

Publication bias is possible but unlikely (Figure 6). This consideration is the result of what was obtained from implementing the Trim and Fill method: since no study was trimmed, the two effect sizes, the estimated (in black) and the observed (in white) coincide. Statistical significance was not reached by either Egger's test ($p = 0.837$) or Begg and Mazumdar's test ($p = 0.573$).

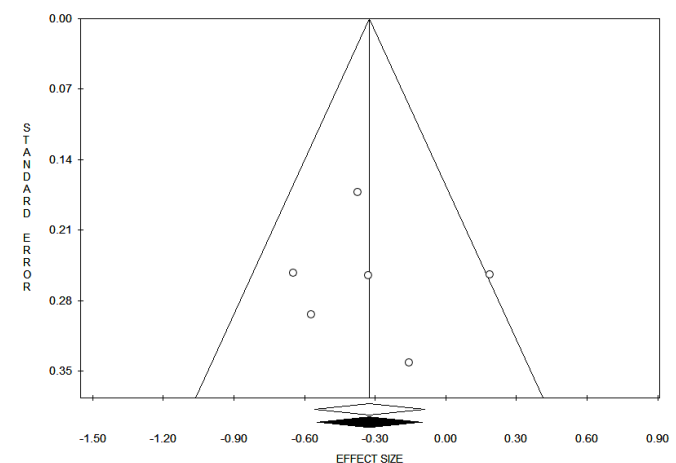


Figure 6: Funnel plot.

Summary of findings

The GRADE evaluation produced a low certainty/quality of evidence for the effect of VR on pain and anxiety/fear in children (Table 4).

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Summary of findings. Virtual reality for procedural pain and anticipatory anxiety in children in Emergency Room.

Virtual reality compared to Standard of care

Patient or population: children (0 to 18) undergoing medical procedures

Setting: Emergency Room

Intervention: virtual reality

Comparison: Standard of care

Outcome	Anticipated absolute effects* (95% CI)		N° of sessions (studies)	Certainty/quality of the evidence (GRADE)	Comments**
	Risk with Standard of care	Risk with virtual reality			
Children procedural pain	-	The mean procedural pain (SMD) level with virtual reality was 0.32 standard deviation lower (0.56 to 0.09 lower).	409 (6 RCT's)	⊕⊕⊕⊖ Low ^{a,b}	This result equates to a small difference in favor of virtual reality.
Children's anticipatory anxiety or fear	-	The mean level of anticipatory anxiety (SMD) with virtual reality was 0.26 standard deviation lower (0.45 to 0.06 lower).	409 (6 RCT's)	⊕⊕⊕⊖ Low ^{a,b}	This result equates to a small difference in favor of virtual reality.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**0.2 represents a small difference, 0.5 is a moderate difference, and 0.8 is a large difference.

CI: confidence interval; SMD: standardized mean difference; RCTs: randomized controlled trials

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect

^a Downgraded once for serious study limitations: trials had some concerns/high risk of bias.

^b Downgraded once for imprecision due to analysis based on < 200 participants per group.

Table 4: summary of findings

DISCUSSION

The objective of this systematic review with meta-analysis was to measure the effect of virtual reality versus Standard of care on procedural pain and anticipatory anxiety in children admitted to the emergency room. The results show that the intervention results in the improvement of both outcomes; although the overall effect size is statistically significant, it is small. The level of certainty/quality of evidence is low, so the actual effect could be substantially different from that estimated. Sensitivity analysis showed that although the small benefit of the intervention is not disproved, the effect size is no longer statistically significant. The risk of publication bias appears unlikely.

Implications for practice

Despite the good results obtained from the intervention on procedural pain and anticipatory anxiety (or fear) in children, it is important to emphasize that: (a) all included studies were carried out in an emergency room of a hospital providing tertiary care and thus providing highly skilled clinical care services; (b) except for one case [47], for all other studies the medical procedures implemented were venous sampling or intravenous cannulation. What was obtained cannot, therefore, be generalised to healthcare facilities providing primary or secondary care or to procedures other than those in the studies. It was not possible to perform subgroup analyses by gender or age, variables that could play a role in the effect of the intervention, along with other child characteristics such as temperament, neurocognitive

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development, previous experiences, coping style, attitudes, and empathy of health care providers [25,56,57].

Although VR is considered a homogenous intervention, due to the lack of shared standards, both the duration of use and the hardware and software used were different, which may have influenced the level of immersion and, thus, effectiveness. The hardware should be customizable according to the age and anthropometric characteristics of the child: the few dropouts recorded by the included studies occurred mainly because, in younger children, the headset did not fit properly or the visor tended to slip off the head or because the interpupillary distance was inadequate, with negative repercussions on the level of immersion and 3D viewing. To date, there is a lack of evidence in favor of the superiority of one VR environment over another [58], although a practical and usable scenario should be attention-grabbing, highly immersive, simple for younger children, and fun for older ones, ethically and culturally sensitive, and appropriate for use in an emergency room [45].

The SoC was also very heterogeneous: it could consist of verbal comfort from caregivers and/or health workers or include alternative distraction techniques and/or the support of the Child Life Specialist (CLS), a professional with a degree in the area of psychology or educational sciences and specialized in the use of effective strategies for controlling children's pain and anxiety. A variable but generally high proportion of participants used a topical analgesic and/or anesthetic prior to the procedure, and in none of the included studies were the times of administration and doses delivered specified. In this sense, both the presence of CLS and the widespread use of topical analgesics or anesthetics may have acted as effect modifiers, making it problematic to discriminate the net benefit of the procedure.

Pain assessment was carried out, consistent with the child's neurocognitive development and age, with

hetero-directed or self-directed scales. However, the former may lack practicality and accuracy as they involve observing the facial expressions of a child wearing the VR visor with much of the face covered [59]. Anxiety was measured with instruments that were not always adequate [60-62]; this may have hindered its proper assessment [5]. Furthermore, in the included studies, anxiety and fear have been treated as synonyms; although in clinical practice, the difference is not always relevant, they are theoretical constructs with profoundly different meanings that should be differentiated more rigorously [25].

Implications for research

Many of the included studies were probably underpowered to detect statistically significant differences; it would therefore be necessary for future studies to be not only of higher methodological quality and low risk of bias but also multicentre and with an adequate sample size for the benefit of greater statistical power and the feasibility of subgroup analysis by gender and age. To test variations on pain and anxiety, several VR scenarios of different durations should be tested, and different types of hardware platforms should be compared [58].

The feasibility of a concrete implementation of the intervention in clinical practice in terms of economic resources should be considered; specifically, the costs for the purchase of VR devices, replacement in case of damage or upgrade, and periodic disinfection of the hardware should be evaluated. Smartphone-based devices are systems with orientation functionality that are generally portable and self-contained and require very little space and set-up time to use, are lightweight, inexpensive, easy to clean, and can have disposable components; systems with orientation and tracking functionality include trackers and sensors and increase the level of interaction but are more expensive and although to some extent still portable, they are heavier, require more time for set-up and





cleaning at the end of use and require sufficient space for children to move around safely [63].

Since CLSs are often tasked with setting up the VR device and supporting the child during its use in the included studies, their perspectives should be considered and included in future research. In order to better clarify the effect size of VR, it would be desirable for future studies to ensure greater homogeneity of the SoC and to specify the timing, doses, and ways of administration of topical analgesics/anesthetics. Finally, little attention was paid to the rare and mild side effects recorded during VR use. The observed symptoms, which include eye fatigue, headache, dizziness, and nausea, are cumulatively related to cybersickness [64]. To explain cybersickness, the currently most accepted theory is that of sensory conflict [65,66]. It traces the cause to a lack of synchronization between the ocular and vestibular systems: this occurs when the senses do not receive the expected sensory feedback in the presence of a real rather than virtual scenario. This determines the fact that children with vestibular abnormalities, seizure disorders, migraines, or headaches may be more at risk for cyber sickness, and therefore, for these individuals, the use of virtual reality is contraindicated [67].

Comparison with other reviews

The comparison with previous systematic reviews was limited to those that focused on the effect of VR for procedural pain from venous sampling or intravenous cannulation [25,26] or that performed a subgroup analysis by type of medical procedure [7,20,22]. These reviews also found a positive and statistically significant effect of the intervention over SoC on pain; a benefit was also found on anticipatory anxiety or fear, but statistical significance was not always reached [7]. In the present review, the effect of VR on the child's anticipatory anxiety or fear appears negligible compared to previous reviews. This could be due to two factors acting in synergy: the small

sample size of the studies (higher risk of false negatives) and the already low levels of anticipatory anxiety or fear recorded in some studies before the implementation of VR, both in the intervention and control group.

Limits

The main limitations, which affect the internal and external validity of the results, include (a) the small number and sub-optimal methodological quality of the included studies; (b) the low overall number of participants (N = 433, of which n = 409 were available for the VR vs SoC comparison), resulting in low statistical power; (c) the impossibility, due to the nature of the intervention, of conducting the studies blinded; (d) the limited nature of the medical procedures examined; (e) the setting where the trial was conducted, for all studies an emergency room of a tertiary care hospital.

CONCLUSIONS

In children admitted to the emergency room, the effect of VR compared with SoC on the reduction of procedural pain and anticipatory anxiety is statistically significant but small; the level of certainty/quality of evidence is low.

Until further research provides more data to confirm the findings, they should be viewed with great caution; at present, they may provide an indication of the effect of the intervention for some medical procedures performed in tertiary care hospitals.

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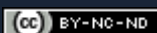


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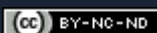


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APPENDIX 1: Search strategy (e.g. MEDLINE)

#1 "Pain"[MeSH]	AND	#2 "Emergency Service, Hospital"[Mesh]	AND	#3 "Virtual Reality"[MeSH]	AND	#6 "Infant"[MeSH]	AND	#10 "Randomized Controlled Trial" [Publication Type]
				OR		OR		OR
				#4 "Virtual Reality Exposure Therapy"[MeSH]		#7 "Child"[MeSH]		#11 "Randomized Controlled Trials as Topic"[Mesh]
				OR		OR		
				#5 "Exergaming"[MeSH]		#8 "Adolescent"[MeSH]		
						OR		
						#9 "Minors"[MeSH]		
OR								
#12 Pain	AND	#15 "Hospital Emergency Services"	AND	#32 "Virtual Reality Immersion Therapy"	OR	#67 Child*	AND	#78 "randomizedcontrolled trial"
OR		OR		OR		OR		OR
#13 Suffering		#16 "Emergency Hospital Service"		#33 "Virtual Reality Therapy"		#68 Infant*		#79 "randomizedcontrolled study"
OR		OR		OR		OR		OR
#14 Ache		#17 "Emergency Hospital Services"		#34 "Virtual Reality Therapies"		#69 Newborn		#80 "randomisedcontrolled trial"
		OR		OR		OR		OR
		#18 "Hospital Service Emergency"		#35 "Educational Virtual Realities"		#70 Neonat*		#81 "randomisedcontrolled study"
		OR		OR		OR		OR
		#19 "Hospital Service Emergencies"		#36 "Educational Virtual Reality"		#71 Baby		#82 rct
		OR		OR		OR		
		#20 "Hospital Emergency Service"		#37 "Instructional Virtual Realities"		#72 Babies		
		OR		OR		OR		
		#21 "Emergency Units"		#38 "Instructional Virtual Reality"		#73 Adolescen*		
		OR		OR		OR		
		#22 "Emergency Unit"		#39 "User-Computer Interfaces"		#74 Youth*		
		OR		OR		OR		
		#23 "Accident and Emergency Department"		#40 "User Computer Interface"		#75 Teen*		
		OR		OR		OR		
		#24 "Emergency Ward"		#41 "User Computer Interfaces"		#76 Teenager*		
		OR		OR		OR		
		#25 "Emergency Wards"		#42 "Virtual Systems"		#77 Minor*		
		OR		OR		OR		
		#26 "Emergency Departments"		#43 "Virtual System"		#78 Pediatric*		
		OR		OR				
		#27 "Emergency Department"		#44 "Computer Simulations"				
		OR		OR				
		#28 "Emergency Room"		#45 "In silico Simulation"				
		OR		OR				
		#29 "Emergency Rooms"		#46 "Computerized Models"				
		OR		OR				
		#30 "Emergency Outpatient Unit"		#47 "Computerized Model"				
		OR		OR				
		#31 "Emergency Outpatient Units"		#48 "Computer Models"				
				OR				
				#49 "Computer Model"				
				OR				
				#50 "In silico Models"				
				OR				
				#51 "In silico Model"				
				OR				
				#52 "ComputationalModelling"				
				OR				
				#53 "ComputationalModeling"				
				OR				
				#54 "In silico Modeling"				
				OR				
				#55 "Video Game"				

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OR
#56 "Computer Games"
OR
#57 "Computer Game"
OR
#58 "Character User Interface"
OR
#59 "Command-line Interface"
OR
#60 "Command-line User Interface"
OR
#61 "Computer User Interface"
OR
#62 "Graphic User Interface"
OR
#63 "Graphical User Interface"
OR
#64 "Text User Interface"
OR
#65 "Text-based User Interface"
OR
#66 "User-computer Interface"

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