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The Impact of Virtual Reality (VR) on Psychological and Physiological Variables in Children Receiving Chemotherapy: A Pilot Cross-Over Study

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Abstract

Background: Virtual reality (VR) is a novel technology which provides a great opportunity to reduce some of the adverse effects of chemotherapy. Objective: Our study aims to investigate the effects of VR on the emotional states of paediatric oncology patients (n = 29, age: 10-18 years) receiving chemotherapy in a clinical setting with a crossover design. Methods: Children played a VR game in the experimental, and a mobile game in the control condition. Psychological (happiness, joy, fear, nervousness, anxiety, alertness, patience) and physiological variables (heart rate, systolic blood pressure, electrodermal activity), as well as pain and nausea were measured before and after the sessions. Data were analysed with multiple 2-way repeated measures ANOVA. Results: Joy ($P = .003$) and happiness ($P < .001$) increased significantly when using VR, while there was no change in the control condition. Anxiety decreased ($P = .002$) and patience increased ($P = .015$) in both conditions, implying no additional benefit of VR. Children were more fearful before the VR session ($P = .005$), which disappeared after it. In case of physiological parameters, electrodermal activity decreased ($P = .01$) significantly after playing the mobile game, but not after the VR one. Conclusions: Our investigation point to the positive effects of VR on mood in paediatric oncology inpatients, thus, it could be used as a new tool in improving patients' well-being during chemotherapeutical treatment. Our results indicate that VR is an effective tool in improving patients' well-being during chemotherapeutic treatment.

Keywords

virtual reality, chemotherapy, paediatric oncology, mood, supportive care

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Introduction

The diagnosis of cancer and antitumour treatments are both psychologically challenging and burdensome for the body, thus the World Health Organization's 'CureAll' global initiative for childhood cancer suggests that both psychological and physical symptoms should be treated with equal priority by multidisciplinary teams.[1] Chemotherapy treatments have undergone important development (eg, protocol improvements due to international multicentre trials to minimise adverse effects and maximise efficacy) in recent years, resulting in the increase in the number of cancer survivors,[2] hence it should be of utmost importance to improve the well-being of these patients and to prevent unfavourable psychological adverse effects, such as anxiety, depression, and post-traumatic disorder.[3]

The significant psychological burden of cancer treatment is the result of different interplaying factors. First, the diagnosis itself has a strong negative impact on the children and their families.[4] Their lives change drastically, as they are losing their independence and their control over events during long-term hospitalisation. Most of the chemotherapy drugs have side effects affecting children's well-being by causing fatigue, weakness, malaise, cognitive changes such as inattentiveness and forgetfulness, as well as by leading to

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unpleasant changes in their appearance (eg, hair loss).[5] Furthermore, living with and being aware of the illness have detrimental effects on the social life and the mental status of the patients. There are many promising ways (eg, cognitive behaviour therapy) for reducing stress in the hospital, however, the cost of individual therapy is high and requires a large number of specialists. Thus, innovative approaches like virtual reality (VR), an artificial 3-dimensional simulated environment, may be a cost-effective and efficient method for stress management and mood improvement in hospital settings.

Recently, VR has been used in three different ways in the field of paediatric oncology to improve the well-being of patients. The first approach aims to reduce the side effects of chemotherapy and hospitalisation.[6] Fewer depressive symptoms were reported using a VR-based therapeutic play session in 8 to 16 years old oncology patients compared to control.[7] Sharifpour et al found improvement in pain variables in adolescents receiving chemotherapy after regularly watching movies in a VR environment.[8] A pilot randomised controlled trial investigated 90 hospitalised children with cancer and compared the same content on different platforms (iPad and Gear VR). No statistically significant results were observed in psychological variables and heart rate (HR), however, there was a tendency for mood improvement in the VR group.[9] The second approach aims to reduce pain and anxiety during acute invasive procedures during cancer treatment (eg, venipuncture, port access). Four studies investigated children with cancer during VR-assisted procedures and found pain reduction measured by self-reported psychological questionnaires[10-12] and by the reduction in heart rate.[13] The third approach uses VR to reduce procedural anxiety by enhancing preparedness for radiotherapy.[14] In sum, using VR during chemotherapy treatment seems to have favourable outcomes, however, there are still outstanding questions regarding the best ways to carry out VR sessions, the content of the VR experience, and the most efficient methods to capture its effects.

VR has a strong distracting effect by means of creating a sense of presence through a multisensory illusion,[15] which may be advantageous in hospitalised patients. The sense of presence is a subjective experience of being in another place than the one where the individual is physically located.[16] Oncology patients who are hospitalised and often restricted in their activities due to their treatment or its side effects could benefit remarkably from an experience helping them feel in control and have access to a different environment, regardless of it being virtual. The sense of presence leads to attention allocation, which contributes to mood improvement, anxiety, and pain reduction, as well as time perception altering effects of VR.[17]

One important factor which might limit the usage of VR in chemotherapy patients is cybersickness syndrome, a type of motion sickness appearing during and after being in a virtual environment. While its exact pathophysiological mechanisms are not clear, the sensory conflict theory (a mismatch between the visual and the vestibular systems) has been proposed as an underlying factor.[18] Due to the fact that most chemotherapies are emetogenic, it is crucial to prevent cybersickness during VR sessions.

Overall, there have only been a few studies about the effects of VR during chemotherapy in children, and none of the studies has used within-subject design in children, which can reduce the interindividual variability emerging from the interaction between the different situations, treatment regimens, and personalities. Moreover, few studies measure physiological variables despite the fact that these parameters could serve as objective indicators of the participants' stress level and may be associated with favourable health outcomes. Thus, we aim to study the effects of VR with a crossover design on several psychological and physiological factors during chemotherapy in order to investigate its usefulness in enhancing the well-being of these patients in a clinical setting. We hypothesised that a VR session can reduce anxiety, nausea, and fatigue, and can improve mood during chemotherapy. Furthermore, we expected that VR can decrease the activity of the sympathetic nervous system indicated by the reduction in heart rate, systolic blood pressure, and electrodermal activity (EDA).

Materials and Methods

Design

A crossover design was used in which all children participated in both the experimental (VR) and the control (mobile game) conditions. The order of the conditions was randomised across participants. A random sequence was generated prior to the start of the study which specified the starting session for the following participant. Sessions were scheduled in a way that each child received the same chemotherapeutical agents in both conditions controlling for the variable effects of the different drugs. The research was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (registration number: 79/2018, registration date: 22.05. 2018.). The children and their parents were informed that participating in the research is voluntary and that they could withdraw at any point without the need to provide an explanation. The parents signed a written consent form at the beginning of the experiment.

Participants

Thirty-five children (range: 10-18 years old) receiving chemotherapy treatment were recruited to our study at the oncology units of the Second Department of Paediatrics, Semmelweis University between August 2018 and February

2020. Forty-three children were approached. Eight children declined participation due to different reasons (not interested in the study, feeling unwell). VR devices are recommended for use over the age of 13 years. We felt that this age could be sufficiently reduced in a controlled environment. We decided to recruit children older than 8 years as they are mature enough to understand the task, and they are able to wear the VR device, as well as to use the controllers without any problems.

The inclusion criteria were: receiving active chemotherapeutic treatment, inpatient in one of the oncology units, 8 to 18 years old, and feeling well enough to participate (based on the opinion of the nursing staff in charge). The exclusion criteria were: any vision problem or eye movement disorder, major neurological illness, or intellectual disability.

VR Condition

The full version of the VR game A Night Sky (Coatsink Software LTD, UK, 2017) was used in our VR condition due to several reasons. First, playing with A Night Sky does not require a sudden change of position which may be important in reducing the risk of cybersickness. Second, the game is completely interactive, the children have to manipulate in the virtual environment with a controller. Interactivity may facilitate the immersive effects of VR, and it may also contribute to the feeling of control.[19] In this game, children have to link stars in a calm, Arctic setting. If the stars are linked properly, mythic creatures appear as a reward.

The game was presented by either a Samsung Gear VR (with Samsung Galaxy S7 Edge, Samsung Electronics Co. LTD, Seoul, South Korea, 2016) or an Oculus Go (Oculus VR LLC, California, USA, 2018). Both devices have 5.5-inch display with 2560 x 1440 resolution, and 3 degrees of freedom motion detection system, therefore, the goggles track only the orientation, not the position, meaning that children could only look around and not move in the virtual environment.

The experimenter followed the actions of the children by streaming the virtual environment using the built-in screen mirror function of the Oculus mobile application to help the children navigate through the game.

Before use, the device was wiped with antiseptic wipes and was introduced to the children by the experimenter (S.E.). The experimenter followed the VR environment by mirroring the environment to a computer screen. The experimenter only made contact with the participants when they needed help.

Control Condition

The children were allowed to choose a mobile game on their mobile phone according to their own preferences. This way, children could choose a game which was the most optimal for their current state, which decreased variance emerging from individual differences.

Measures

Heart rate and systolic blood pressure (SBP) were measured using an automatic blood pressure monitor on the upper arm. Electrodermal activity was measured by Obimon, using a 22-bit resolution analogue-to-digital converter, a zero-drift operational amplifier on the input signal and a constant voltage EDA method. The electrodes were directly attached to the device. EDA provides information about the activity of the sympathetic nervous system.[20]

Psychological variables (happiness, joy, fear, nervousness, anxiety, alertness, patience, pain, and nausea) were measured by numeric visual analogue scales, which proved to be reliable tools for children.[21]

Procedure

Physiological variables were measured right before and after the experiment. First, heart rate and systolic blood pressure were taken, which were followed by capturing electrodermal activity for 3 minutes on the surface of the palm with the Obimon device in a still, sitting position. Afterwards, the children filled out the questionnaire. Each condition lasted a maximum of 30 minutes and took place in the hospital bed of the children in the afternoon. The same measurements were taken (HR, SBP, EDA, and questionnaire) after the session.

Data Processing

Raw skin conductivity was measured every 125 ms. Artefacts were manually excluded according to Kocielnik et al.[22] More than 0.5 μs second-to-second rise and drop in the baseline skin conductance level (SCL) was omitted too. Because of the large individual variability, a minimum of 0.01 μs and a maximum of 100 μs SCL filters were applied.

Statistical Analyses

Statistical analyses were performed with R (R version 3.6.1, R Core Team R).[23] Normality was checked by visual inspection. Variables with right-skewed distribution (happiness, joy, anxiety, fear, nervousness, patience) were squared, while left-skewed distribution (EDA) was square root transformed for analysis. To compare questionnaire data and physiological parameters before and after the intervention by condition, multiple 2-way repeated measures ANOVA were performed with time (before, after) and condition (VR, control) as independent variables with the anova_test function of the rstatix package. Repeated measures ANOVA was used to handle the interrelated data structure due to the

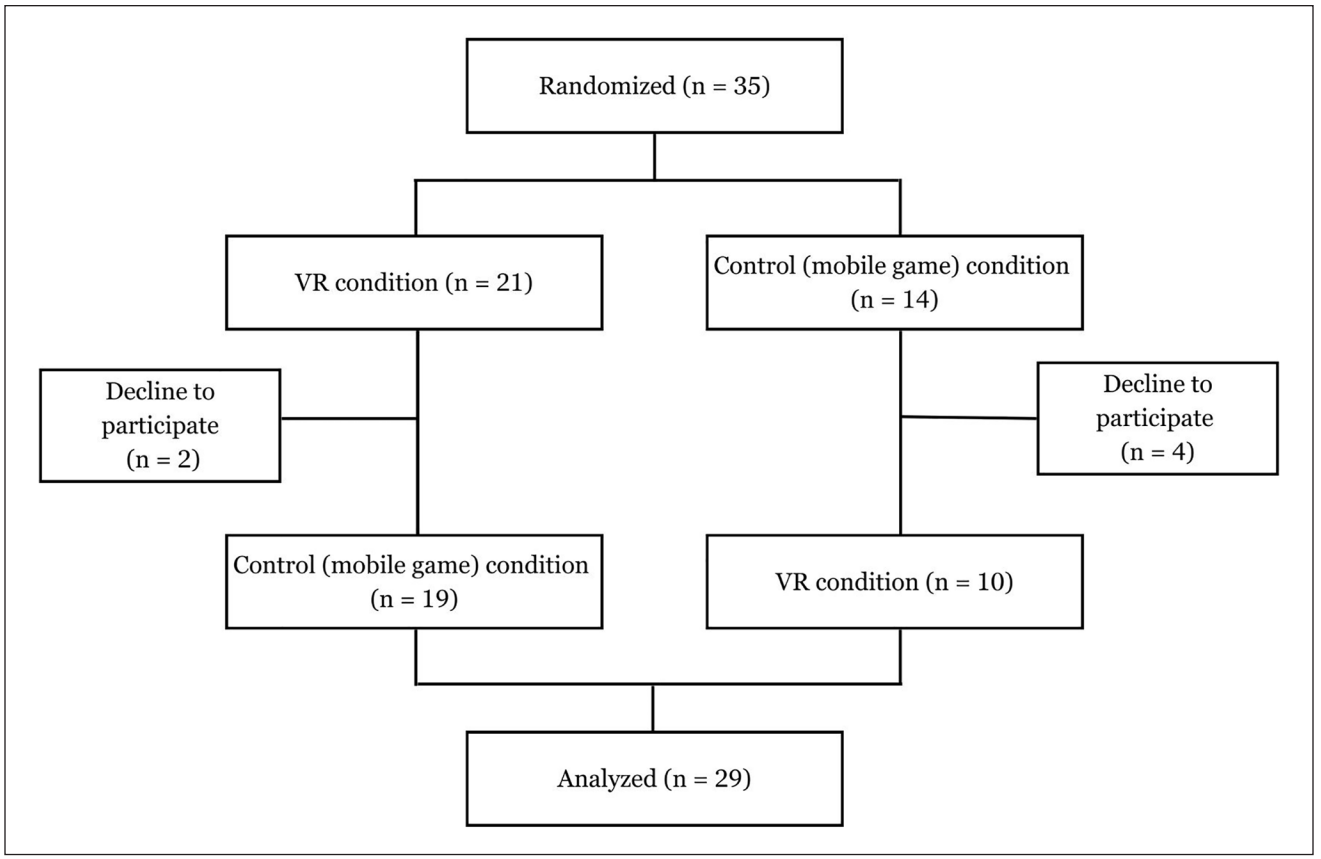

Figure 1. Participant flow-chart.

crossover design. If a significant interaction effect was found, post-hoc paired t-tests were performed. The change in pain and nausea scores were recorded into three categories (decreased, no change, and increased) and analysed with ordinal logistic regression.

Results

Baseline Characteristics of Patients

The data of 29 children (female: 8, male: 21) were analysed. Six children (female: 3, male: 3) were excluded from further analyses as they did not take part in both conditions due to cybersickness syndrome (1 patient), change of hospital (1 patient), and incomplete questionnaires (4 patients). The mean age of the excluded children was 13.66 years (SD = 3.61 years). Four children dropped out after the control, 2 after the VR condition. The participant flow-chart can be seen in Figure 1.

Mean age was 15.28 years (SD 2.44 years, min = 10.28 years, max = 18.69 years). The patients were receiving chemotherapy for ALL (9), Hodgkin-lymphoma (8), osteosarcoma (4), Ewing-sarcoma (3), non-Hodgkin lymphoma (2), germinal cell tumour (2) and rhabdomyosarcoma (1). Four participants had a relapsed disease. Participants were randomly assigned to start with the control or the VR condition (10 and 19, respectively). Median difference between the first and the second occasion was 27 days (IQR 24 days). Mean duration of the sessions was 22.50 minutes (SD 3.43 minutes). Mean time interval since diagnosis was 106.3 days (IQR 54 days), while mean length of hospital stay immediately before intervention was 2.45 days (IQR 2 days), meaning that these children were in the middle of their treatment regimen.

Effects of VR on Psychological and Physiological Variables

For happiness and joy, a significant main effect of time (happiness: $F(1,28) = 16.54$, $P < .001$, eta squared = .046, joy: $F(1,28) = 9.07$, $P = .005$, eta squared = .036) and significant interactions of time and condition (happiness: $F(1,28) = 10.56$, $P = .003$, eta squared = .031, joy: $F(1,28) = 6.68$, $P = .015$, eta squared = .01) were found. Post-hoc tests revealed that a significant increase in happiness ($P < .001$) and joy ($P = .003$) were found only in the VR condition. Main effect of condition was not significant for either case. For fear, a significant main effect of condition was revealed ($F(1,28) = 4.78$, $P = .037$, eta squared = .029), interaction between time and

Table 1. Summary of the Main and Interaction Effects of the Repeated Measures ANOVA.

	Main effects						Interaction effect		
	Condition			Time			Condition × Time		
	F	*P*	Eta squared	*F*	*p*	Eta squared	*F*	*P*	Eta squared
Happiness	0.04	.838		16.54	<.001	.046	10.56	.003	.031
Joy	0.28	.602		9.07	.005	.036	6.68	.015	.01
Fear	4.78	.037	.029	3.4	.076		2.16	.153	
Nervousness	0.41	.528		2.94	.098		0.1	.759	
Anxiety	2.7	.112		11.43	.002	.03	1.08	.307	
Alertness	0.44	.514		1.67	.207		0.18	.673	
Patience	3.43	.075		6.66	.015	.019	0.001	.97	
Heart rate (minutes^{-1})	0.617	.439		0.06	.916		0.71	.407	
SBP (Hgmm)	0.07	.787		0.09	.772		1.51	.23	
EDA (μS)	1.78	.193		7.16	.012	.008	4.97	.034	.008

df = 1, 28.
Eta squared is not presented if the effect was not significant.

condition and the main effect of time were not significant. Post-hoc tests showed that, when participating in the VR condition, children were more fearful before the intervention than when participating in the control condition ($P = .005$). There was no difference between the conditions after the intervention ($P = .276$). For anxiety and patience, a significant main effect of time was found (anxiety: $F(1,28) = 11.43$, $P = .002$, eta squared = .03, patience: $F(1,28) = 6.66$, $P = .015$, eta squared = .019), the interaction between time and condition and the main effects of the condition were not significant, meaning that anxiety levels decreased, whereas patience levels increased after the intervention similarly in both conditions. There were no significant main or interaction effects found for nervousness or alertness.

In case of the physiological variables, there were no significant main and interaction effects in HR and SBP. There was a significant main effect of time ($F(1,28) = 7.16$, $P = .012$, eta squared = .008) and interaction effect of time and condition for EDA ($F(1,28) = 4.97$, $P = .034$, eta squared = .008). The main effect of condition was not significant. Post-hoc tests revealed a significant decrease in the control ($P = .005$) and no significant change in the VR condition ($P = .993$). The summary of the main and interaction effects are presented in Table 1. Mean differences with 95% confidence intervals with post-hoc paired t-tests by conditions are presented in Table 2.

To check whether the order of the intervention has any effects, 3-way mixed effects ANOVA was performed on all of the above variables. No significant 3-way interaction was found.

Pain and nausea

The changes in pain and nausea scores were analysed with ordinal regression. Condition was not a significant predictor for either the change in nausea (beta = −0.14, $P = .81$, OR = 0.87, 95% CI 0.26 2.81) or the change in pain (beta = 0.31, $P = .698$, OR = 1.37, 95% CI 0.28 7.53).

Discussion

Research about using VR in paediatric oncology settings is still in its infancy. Studies are inconclusive about the positive effects of VR, moreover, there are outstanding questions regarding the best ways to capture its impact, as well as about the most important features of its delivery. In our research, a crossover design was used in paediatric oncology inpatients to reduce the variability induced by interindividual differences. Children participated in both a VR and a control (mobile game) condition during chemotherapy on different occasions. Variables regarding the children's emotional states and physiological measurements of stress response (HR, SBP, EDA) were compared before and after the interventions.

Our findings confirmed our hypotheses regarding two variables associated with mood - in the VR condition, children indicated increased scores both in happiness and joy after the intervention; meanwhile, there was no change in the control condition. These results are congruent with the study of Li et al in which patients reported fewer depressive symptoms after attending therapeutic VR play sessions for 7 days.[7] Furthermore, our findings support the observed tendency for the larger mood improvement in Tennant et al.[9] Anxiety decreased in both conditions, implying no additional benefit of VR compared to control. Similarly, patience increased in both conditions after the intervention. In addition, children were more fearful before the VR condition, whereas there was no significant difference after the interventions. Importantly, scores for both anxiety and fearfulness were

Table 2. Mean Differences With 95% Confidence Intervals by Condition and Post-Hoc Paired *t*-Tests.

	VR			Control		
	MD	95% CI	*P*-value	MD	95% CI	*P*-value
Happiness[a]	22.21	11.39 33.03	<.001	2.34	−3.8 8.49	.441
Joy[a]	16.59	6.09 27.08	.003	5.14	−1.19 11.47	.108
Fear[a,b]	7.72	−0.58 16.02	.067	0.21	−4.77 5.18	.932
Nervousness[a,b]	7.48	−5.57 20.54	.25	5.41	−1.08 11.91	.099
Anxiety[a,b]	15	2.78 27.22	.018	6.9	−1.21 15	.092
Alertness	0.52	−0.46 1.49	.286	0.28	−0.44 0.99	.438
Patience[a,b]	8.72	−2.51 19.96	.123	8.45	−0.56 17.46	.065
Heart Rate (minutes^{-1})	0.62	−2.8 4.04	.713	−1.24	−4.86 2.38	.488
SBP (Hgmm)	1.17	−1.78 4.13	.423	−1.86	−5.83 2.1	.344
EDA (μS)[c]	0.02	−5.18 5.23	.993	−10.17	−17.03 −3.32	.005

Abbreviations: MD, mean difference; CI, confidence intervals; SBP, systolic blood pressure; EDA, electrodermal activity.
[a]Squared for analysis.
[b]Reversed scale.
[c]Square root transformed for analysis.

rather low. This way, the higher anxiety and fear, as well as lower patience levels before the intervention may be explained by the excitement experienced by children. However, it is also possible that the interventions reduced anxiety and made children more patient by means of the distracting effects of either games, or the interaction with the experimenter. Notably, tiredness, pain, and nausea did not differ between the conditions and did not change after the interventions, meaning that VR caused neither cybersickness in most of the cases, nor increased tiredness sometimes reported by VR users.[24] However, we should take into account that one child dropped out from the experiment due to cybersickness.

As for physiological parameters, EDA decreased significantly after playing the mobile game, but not after the VR session. This might reflect excitement before the session similarly to the anxiety and impatience experienced that diminished after playing a mobile game. The fact that the mobile game was chosen by the children, hence was familiar to them, could contribute to the disappearance of the excitement. No significant changes were found in heart rate or systolic blood pressure. The reduction in heart rate was only noticed during acute procedures, but not during chemotherapy or hospitalisation.[13] A single VR session may have a more prominent effect in reducing an acute stress reaction than a more chronic type of stress. This might be true for psychological variables too, for example, Sharifpour et al found that repeated VR occasions resulted in less pain during chemotherapy.[8] Therefore, future research should address whether repeated VR sessions lead to various physiological and psychological changes during chemotherapy.

There are some limitations of our study. The most important one is that the experimenter was not blind to the condition of the participant and the aim of the study, therefore, they might have unconsciously influenced some participants. However, due to the nature of the experiment, it would have been impossible to mask the condition of the patient from the experimenter. Moreover, the second condition was further down the chemotherapy treatment path, therefore, participants may have been in different mental states and experienced different side effects by that point. However, we counterbalanced the order of the intervention and also found that the order did not affect our results In addition, due to data acquisition mistakes the detailed characteristics of the children who declined participation are unknown. Finally, the novelty of VR may generate a placebo effect in patients; future studies should evaluate whether the positive effect remains with the repeated and longer use of VR, as well as to investigate whether repeated and longer use leads to more side effects.

Furthermore, our goal was to form an impression of how well VR could be implemented into paediatric oncology centres. We had a favourable experience, children were enthusiastic about trying VR and mastered the necessary skills quickly. Moreover, parents and staff were also supportive about our intervention. Despite not collecting objective data on this, we had the subjective feeling that our intervention did not disturb any hospital routines, thus, we could easily fit in the VR sessions to the everyday hospital life. However, there may be still problems which can hinder the widespread implementation of VR in clinical practice. First, currently the cost of such devices are relatively high in one amount, however, it can be pay off in the long-term. Moreover, the size of the current devices are large especially for younger children. Furthermore, there is a learning curve in acquiring the skills needed to navigate in the VR environment which can be frustrating for the younger ones without someone guide them through. Nevertheless, these

factors may improve with further technological development and hopefully stop acting as a barrier.

In conclusion, our results confirm the positive effects of VR on mood in paediatric oncology inpatients, indicating that it could be a new tool in improving patients' well-being during chemotherapeutic treatment. However, further research is needed investigating whether these effects are long lasting, which may be a key point according to previous study.[25] The impact and side effects of long-term use of VR are also a crucial area for future research. Using other physiological parameters (eg, heart rate variability) may paint a more accurate picture about the stress level of the participants.

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Author Contributions

Conceptualisation, K.H. and S.E.; methodology, K.H. and S.E.; formal analysis, K.H. and S.E.; investigation, S.E.; resources, K.H. and S.E.; data curation, K.H. and S.E.; writing—original draft preparation, K.H. and S.E.; writing—review and editing, K.H. and S.E.; visualisation, K.H. and S.E.; supervision K.H..; All authors have read and agreed to the published version of the manuscript.

Declaration of Conflicting Interests

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (registration number: 79/2018).

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Data Availability Statement

Data is available upon request from the corresponding author.

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