

## Application of a virtual reality prototype for pain relief of pediatric burn in Taiwan

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### **Application of a virtual reality prototype for pain relief of pediatric burn in Taiwan**

**Aim.** This study examines the usability and effectiveness of virtual reality in reducing pain in wound-care procedures for pediatric burn patients in Taiwan.

**Background.** Virtual reality has continuously gained prominence in the medical arena, for instance, the telepresence for surgery, the management of mental health disorders and pain control of the paediatric burn. Notwithstanding an increased application of virtual reality in the medical arena in North America, there have been no studies investigating its use for paediatric burn patients in Asia.

**Methods.** This descriptive study has two phases: Phase I: the development of a virtual reality prototype. Phase II: the implementation of the prototype to discern its usability and efficacy with paediatric burn patients at a local hospital.

**Results.** The findings suggest that a significant difference is found in the children's reported pain, with or without the virtual reality intervention, over the three phases: before, during and after the dressing change. However, less pain was noted in the intervention group during and after the dressing change.

**Conclusion.** Adding to the existing clinical value of virtual reality identifies the nature of and different children's responses to pain with the use of virtual reality.

**Relevance to clinical practice.** This study is significant since it demonstrates a difference in the child's response to pain based on the nature of presence and distraction. Moreover, given the evidence that a decrease in anxiety was experienced after the dressing change with virtual reality intervention, timing of using the virtual reality intervention before the child develops conditioning anxiety and anticipated pain for the procedure would be of importance.

**Key words:** nurses, nursing, pain and presence, pediatric burn, virtual reality, wound care

## Introduction

Patients with burns suffer both physical and psychological distress resulting from the initial trauma of the injuries. Such distress becomes their daily background pain. Background pain refers to the burn pain experienced by the patient at rest. Apart from the background pain, the pain experienced from the procedure of caring for the wounds is known as procedural pain. This pain occurs during and after wound care (Abdi & Zhou 2002). The burn pain and wound-care procedures often elevate the patients' anxieties, which exacerbates their perception of pain (Chapman 1985). The experience and the amount of pain endured by patients through the wound-care procedure for burns has been documented as being excruciating, despite the administration of the maximum allowable dose of opioid analgesic. The findings in Perry *et al.*'s study (1981) revealed that over 86% of burn patients reported feeling pain with the use of standard levels of opioids during wound care. This phenomenon remains a major issue for burn victims (Everette *et al.* 1990) and is especially disconcerting when the sufferers are young children (Perry *et al.* 1981) despite current advances in the analgesics available to children. One of the major concerns with children who are suffering from burns is their fear of painful procedures. Unlike adults, many sedative drugs will cause more anxiety in children than their intended pharmacological effect (Ahmadi 2001). Children typically also experience a high level of anxiety before and during wound-care treatment for burns (Mcclam 2000). Compounding this concern is the strong conditioned responses of children to the stimuli associated with wound-care procedures for pain (Patterson 1995). If controlled, this may lessen a child's feelings of anxiety, particularly about the burn wound treatment procedure (Abdi & Zhou 2002). Conversely, without adequate and appropriate pain management, the experience of pain can significantly affect a child's immediate and long-term quality of life and his/her well-being (Das *et al.* 2005).

Since, pain is not only a sensory experience but an affective and cognitive experience as well, pharmacological treatment alone may be insufficient to relieve all discomfort. An

investigation into non-pharmacological methods of pain relief to supplement traditional pharmacological analgesia in children with burns is warranted.

Play, as a form of therapy for children, has long been employed. The use of videogames and virtual environments (VEs) in studies involving children has shown positive results for pain management (Hoffman *et al.* 2000, Ahmadi 2001). However, there is empirical evidence that the use of a 3-D immersive virtual reality (VR) environment is dramatically more effective than other video games, e.g. Nintendo64, in burn wound care sessions, especially with children and adolescents (Hoffman *et al.* 2000), or other cognitive-behavioural techniques, such as listening to music or watching a video (Tan 1982, Geisser *et al.* 1995). The convergence of multi-sensory inputs of VR gives the participants a stronger illusion of 'presence' in the VE through immersion and involvement.

## Background of pediatric burn in the west and the east

Burn injuries afflicted more than a million people in the US annually with a third of the cases being children. Scald injuries are the major cases of accidents for the 0–3 age group and flame burns are most common among children over 3 years (Merz *et al.* 2003). At Harborview Medical Centre in the University of Washington, a third of the burn centre patients are children. Adjunctive treatment to pharmacological therapy has been conducted through the use of VR for adolescent burn pain during wound care with positive results (Hoffman *et al.* 2000). Since, VR has been recognized for its possible value in altering perceptions of pain, this study examines its usability and effectiveness in reducing pain in the dressing change procedure for pediatric burn patients in Taiwan.

In Taiwan, burn injuries account for the most costly non-fatal injuries that are suffered. The notion of cost is not only reckoned in the monetary sense, but in terms of human suffering. The changing of dressings for burn wounds is by far the most painful of that for all wounds, especially for children. Like other countries, Taiwan has a similar epidemiological

distribution among the young, with the age distribution of burn patients peaking at the age group of 0–5 years old (Chien *et al.* 2003). Tung *et al.* (2005), from findings similar to those from the survey conducted by the Childhood Burn Foundation of the Republic of China, revealed that the highest risk age group, for young people to suffer from burns, is between 0 and 9 years old. In Hong Kong, pediatric patients under the age of 15 accounted for 51.7% of admissions in an epidemiological study of hospitalized burn patients in a tertiary burn centre (Ying & Ho 2001). The research team proposes that the findings from the west on the effect of VR as a means to control the pain from wound-care procedures for burns be used as a reference. Young, burned victims in Taiwan may also benefit from the use of VR.

### The concept of virtual reality

The VR is generally defined with reference to some technological instruments, which consist of a computer system that can generate a 3-D real-time animation and a head-mounted display equipped with a position tracker and a data glove (Riva & Mantovan 1999, Vincelli *et al.* 2001).

For the purpose of this study, a design of a basic VR system with super-high-resolution 3-D glasses as an output device that communicates with a computer and an input/control device such as a mouse was used. In view of the lighter weight of the glasses, it was hence chosen for the pediatric group instead of the traditional head-mounted display. An image was generated by the interactive glasses (I-glasses), which is in full colour and has a wide field of view. To the best of our knowledge, thus far, only a few pieces of software for VEs designed for the caring of burn wounds have been developed. Hence, the main program used to create the virtual objects in this study was developed from Visual C++6.0 and DirectX 7.0a SDK. 3-D modelling tools (3D Studio MAX and Rhinoceros).

When the VR was implemented clinically, it referred to the interface of the physical environment and the sensory manifestation. In this study, the child visualized the graphic animation on the I-glasses and acted in the animation via a mouse. In other words, the user acted in an illusion with his/her internal model of action. This illusion was capable of producing a sense of presence only through the user's immersion and involvement in the simulated environment.

## Method

### Study design

This research is a descriptive exploratory study. It was conducted in two phases. Phase I consisted of the develop-

ment of the prototype. Phase II, the preliminary clinical application of the prototype to relieve the pain of pediatric patients when the dressings of their burn wounds were changed, its usability and presence quality, were examined.

#### *Phase I: development of a virtual reality prototype*

The design of the game took into account the children's age group, their psychomotor developmental abilities, the intellectual capabilities of the prospective players and the complexity of the game. A visual display of an ice-cream factory and auditory senses were constructed. The convergence of a multi-sensory input with sound and sight in the VE would create a sense of 'presence' in the environment, with immersion and involvement from the subjects. Hence, it could increase the amount of attention the patient places on the game, the VE. The subjects were told a brief story about their role as a patrol person for an ice-cream factory. The sensation of cold (from an ice-cream factory) may engender the suggestion of pain relief from an experience of being burned (Hoffman *et al.* 2001). The graphic had an initial order of things in the scene, but the orderliness was quickly broken by a fox. To restore orderliness as part of their patrol duties, the subjects would have to scare the fox away by shooting it with ice cream. But they would have to exercise care to avoid shooting a little girl by mistake. All of the motions were designed to be in a continuous flow. An input device with the use of a mouse facilitated ease of control through a gentle pressing movement. Hence, abrupt and possibly jerky movements from the manoeuvre were minimized. Given the need to use a mouse, pediatric patients with burns on their dominant hands were excluded. The wearing of VR glasses, which would block visual cues during the procedure of wound care, might improve analgesia by reducing the patients' strong conditioned responses of anxiety to the negative visual cues associated with the wound care procedure.

#### *Phase II: implementation of a preliminary clinical trial on relieving pediatric burn pain*

*Recruitment of subjects.* The patients were recruited from a major regional burn facility in Taiwan where they were hospitalized. Demographic data and the clinical profiles of the subjects were collected. There were eight eligible patients (seven boys and one girl) in the sample. The mean age for both boys and girls was 6.54 (SD = 2.27). Seven (87.5%) had been scalded and one (12.5%) had been burned. The affected areas were primarily the lower parts of the body, with the exception of two cases. One was on the neck and the other was on the face, close to the chin. With regard to the severity of burns, five (62.5%) had second-degree burns, one (12.5%)

had first-degree burns and one (12.5%) had fourth-degree burns. All of the patients who were enrolled in the study had experienced burns for the first time.

### Ethical consideration

Since, the participants were minors, an explanation of the study was given to their parents and their consent for their children to participate was subsequently solicited. The participation of the children was also voluntary. Both parents and children were informed that the game would be stopped immediately upon any untoward symptoms experienced. Ethical approval for a collaborative study was obtained from the Hong Kong Polytechnic University, the Chang Gung University and the Chang Gung Memorial Hospital. Since, the prototype was developed in Hong Kong, ethical review was therefore obtained.

### Intervention procedure

A crossover design was used and the experimental group served as its own control. The use of a within-subject design enabled there to be the same drug dosages in the VR and the control conditions for each individual patient. The order in which the treatments were administered was carried out by simple number randomization. The patients who participated in the study were on their third–fifth day after the burn incident and during a stay in the hospital that lasted from six–nine days, respectively. The children had all experienced having their dressings changed with no VR. They all had prior anxiety with the dressing change procedure because of their memory of the pain involved. Each of these patients participated in a single VR trial, i.e. once with VR and once without VR.

With the introduction of the VR intervention, the equipment was shown to both the patient and the nurse. The same nurse was involved in the wound-care procedure of a particular patient for the interventions with VR and without VR. All of the nurses involved in the study had a mean of six years of experience in working with burn patients.

The conventional routine protocol of changing the burn wound dressings for the patients was maintained as the control condition. A standard pharmacologic analgesic, as part of a standing order for injectable Demerol and oral Tylenol, was administered to patients after the nurses discussed with the parents and the child about their preference. Their selection of analgesia was not affected by their participation in this study. All of the participants chose oral Tylenol, which was administered 30 minutes before the

dressings were changed, as the conventional measure. The experimental condition consisted of the conventional treatment for pain along with the use of VR during the dressing change procedure. The process of changing their dressings (15–20 minutes) included removing the adhesive tape/bandages and the sulfasil dressing, cleansing the wound and applying a fresh dressing after an assessment by the doctor.

All of the patients were taught how to play the VR game and were allowed to play from 5–15 minutes to get accustomed to the equipment prior to the wound-care procedure and while the nurse preparing the dressing tray.

### Data collection

For both the control and the experimental conditions, the children were asked about their level of pain as measured through the faces scale (Bieri *et al.* 1990). This faces scale is easily used with school aged children and has good psychometric properties. In this measure, the child is required to choose a picture of a face with expressions of various gradations of pain with a scale rating from 0–100 before, during and after the changing of his/her dressings. The nurses were interviewed for their assessment of the children's behaviour through their observations of the children who underwent the wound care procedure. Behavioural observations in conjunction with the child's self-report of the pain felt as his/her dressings were changed are thought to be more sensitive at evaluating the child's distress than any one method alone (Huth & Moore 1998). In the experimental condition, the research nurse would ask the children questions, with or without help from the parents, from the usability and modified presence questionnaires (PQ) after the child responded to the pain ratings. The usability questionnaire consists of items pertaining to the physical comfort of the hardware and the ease of its use. The PQ has a seven-point response scale, which is based on the semantic differential principle (Singer & Witmer 1994). Each item has opposite descriptors at both ends. For this study, a back translation of the questionnaire was conducted for the Chinese subjects. Validation of the contents of instrument was conducted by the experts, based on our study objectives. A reliability analysis was performed on this questionnaire (Dyer *et al.* 1976, Lampton *et al.* 1994, Witmer *et al.* 1996), with a reduction from 32 to 19 items. The reduction was done based on an iterative approach, dropping those items that did not contribute to the reliability of the scale, which yielded a reasonable Cronbach's alpha value of 0.88 (Witmer & Singer 1998). How much presence the children would or did experience in an artificial environment could provide further data for the analysis of the usability of the prototype

and the assessment of the pain relief it afforded. There was also a semi-structured interview for 15 minutes conducted with the same nurse for each patient on her perception of the usability of the VR and its effect on the patient's pain relief in both the control and experimental conditions.

## Data analysis and results

The quantitative data from the self-reported faces pain scale, usability and PQ were entered into a SPSS data file for analysis. The mean pain intensities (SE) for the non-VR and the VR groups are shown in Table 1.

Using the paired *t*-tests, there was no significant statistical difference found before ( $df = 7$ ,  $t = 0.37$ ,  $p > 0.05$ ), during ( $df = 7$ ,  $t = 1.58$ ,  $p > 0.05$ ) and after the dressing ( $df = 7$ ,  $t = 0.64$ ,  $p > 0.05$ ) change of the groups with the intervention of VR and with no VR.

One-way ANOVA with *post hoc* test was performed to examine the difference in pain intensity among the three phases for the two interventions separately. Significant differences in pain intensity were found in both groups (no VR group:  $F = 5.70$ ,  $p = 0.01$ ; VR group:  $F = 3.82$ ,  $p = 0.04$ ). For no VR, the pain reported during the procedure was of a significantly higher intensity than that reported before (mean difference = 42.50,  $p = 0.01$ ) and after the procedure (mean difference = 35.00,  $p = 0.02$ ). For VR group, the pain reported during the procedure was of a significantly higher intensity than that reported before (mean difference = 26.88,  $p = 0.03$ ) and after the procedure (mean difference = 29.38,  $p = 0.02$ ). Evaluation of the mean difference between the two groups suggests that less pain seems to be experienced in the group with VR intervention during and after the dressing change though there is no statistical difference from the paired *t*-tests in Table 1. This result also supports the nurses' observations that there was a significant improvement in the children's anxious behaviours with VR intervention in the qualitative data from the nurses' interviews that will be described later in this paper.

**Table 1** Distribution of the mean and standard error of the reported pain intensity before, during and after the dressing change with ( $n = 8$ ) or without the use of VR ( $n = 8$ )

	Before	During	After
With VR	11.25 (7.43)	38.13 (12.02)	8.75 (2.95)
Without VR	11.25 (6.39)	53.75 (11.80)	18.75 (9.53)
<i>P</i> (paired <i>t</i> -test)	$p > 0.05$	$p > 0.05$	$p > 0.05$

VR virtual reality.

## Presence questionnaire

Despite a lack of significant correlation between the reported pain intensity 'during' the dressing change and the mean presence 4.81 (1.05), the clinical improvement was found in the observations of children's behaviours from the nurses' interviews.

## Usability of the prototype

Regarding the usability of the prototype, the mean for each question (SE) was as follows: the ease of operation was 3.13 (0.718), ease in learning was 3.5 (0.802), comfort level of the glasses was four (0.598), its weight being heavy was 3.38 (0.498) and would play the game again was 4.63 (0.460).

## The virtual reality effect on background, procedural pain relief and anxiety

In the interviews, the nurses described that the children's reactions were governed by the temporal sequence of this wound care procedure: before (the removal of the bandage), during (the cleansing of the wound and the application of the medication dressing) and after (after the re-bandaging). The sequence served as negative cues and was aversive conditioning. The general behavioural responses to avoid the dressing change process, among this group of children under study without the VR intervention, were pushing the nurse's hands away, tensing and stiffening up the body, crying vigorously and kicking at times. With the VR intervention, it seems that all of the children were quite involved and immersed in the game before the procedure. While all of the subjects fixed most of their attention on the dressing change procedure during the conventional treatment, with the use of VR and the conventional approach, the subjects demonstrated a shift in attention from their pain albeit with different degrees of effectiveness.

With the VR intervention, even when the children were not totally immersed in the game during the changing of their dressings, their behaviour and emotions were better managed and controlled after the dressings had been changed. The following interview responses from the nurses are illustrative:

*During the time with the VR intervention, the child would not try to move away. When I started to cut the bandage, he would still be playing by moving the mouse. During the process, he would respond to me but only with a word or two, as he seemed to be immersed in the game. This kid told me that he would like to play again the next time. Without the VR intervention during the changing of the dressing, he would be very anxious and would attempt to push my*

*hands away and stiffen his body and a long time would also be needed for the parents to calm him down afterwards. This would take 1–2 hours.*

*Initially, he was very immersed in the game. However, when I started to cut his gauze, he began to stop moving the mouse. With encouragement, he resumed playing. During the process, he was able to play and co-operated with me in terms of changing position. After I had completed the changing of his dressings, he verbalized that he would like to play some more. He played for another 10 minutes, then his parents took him out for a walk. Without the VR, this child would focus on the wound, his facial expression would be tense, his body stiff and he would need to lie down in bed for 15 minutes until he felt less anxious.*

*This child was very attentive when playing for 5 minutes, but when I started to cut the gauze, he began to cry, his body stiffened and he wanted to remove the glasses. I coaxed him and changed the dressing quickly. But as soon as the dressing was almost completed, the kid wanted to play the game again. He stopped crying and was calm and played for another 2 minutes. In comparison, during the time without the VR intervention, his emotions were out of control and he continued to cry after I had completed the changing of his dressings. It took a long time for his parents to calm him down.*

## Discussion

Given the intervention of VR, the significant changes in the children's anxiety during the process and their relative calmness after the changing of their dressings, as well as their wish to continue playing the game afterwards, seem to point to the effectiveness of VR in relieving their pain and anxiety. The children's reduced anxiety, after the dressing change, would have shaped their perceptions of pain the next time their dressings are changed. Moreover, while there was not a total 'presence' (i.e. immersion and involvement) an effect from the VR intervention in terms of various degrees of immersion-involvement and a simple form of distraction was observed in the children's behaviour and from the comments of the nurses.

Witmer and Singer (1998) contended that both involvement and immersion are required for the experience of presence. Involvement is defined as the focusing of one's attention and energy on a coherent set of VE stimuli. Immersion refers to the perception of oneself as a part of the flow of the VE stimulus. Hence, if the children were immersed and involved, they would have placed themselves in the role of the patrol character to chase away the foxes while trying to avoid shooting the girl in the VE. In this respect, immersive VR differs from simple forms of distraction (e.g. video movies, interactive video games) by drawing

more of the children's attention into the VE. With less attention available for evaluating nociceptive input, the child would subjectively experience less pain than otherwise. Hence, an increased level of immersion would translate into an ability on the part of the child to control his/her attention, focusing on what is going on in the VE while ignoring other interferences from the surrounding environment. This level of immersion may enable the [child] to experience more presence and vice versa. In the case of the wound care procedure, some children were not able to remove their attention from their surroundings and have their attention drawn into the VE. To develop a sense of presence, the child needed to focus his/her attention on a meaningful stimulus (Witmer & Singer 1998). In this study, the children seem to have developed a meaningful understanding of the sequence that caused a discontinued flow of some of their involvement in the game. This discontinuity was manifested as a shift in their attention from the game, as some of them exercised selective attention upon the removal of their bandages by the nurse. Selective attention depicts a tendency for a person to focus on selected information that is meaningful and of particular interest to them (Witmer & Singer 1998). The continuity of the sequence of changing the dressings was connected to an associated level of pain and fear. Unfortunately, the conditioned fear/anxiety and anticipated pain became more meaningful as part of their previous experience and the natural response of the children were to avoid the experience.

The children experienced different degrees of immersion and involvement (presence) with the VR intervention could be categorized as total, partial presence and simple form of distraction. In the first two categories, a nurse who cared for a child in both the control and the experimental conditions described the child as 'immersed and involved'. The child was totally oblivious to the fact that the dressing procedure was completed. Others exhibited partial presence in the VE with slight movements after the removal of their bandages, but continued to play. For the latter group, a simple form of distraction manifested itself as a critical shift in the child, from playing with the game to becoming very anxious when he/she realized the nurse was cutting the bandage of the dressing. Witmer and Singer (1998) assert that 'Whether there is a threshold for the allocation of attentional resources that must be reached before the presence is experienced remains an open question, but it is reasonable to assume there is a threshold and that the increased allocation of attentional sources beyond this threshold will result in a heightened sense of presence (for pain relief)' (p. 226). One possible reason for the lack of a significant correlation between the reported pain intensity 'during' the

dressing change and the mean presence may be related to the size of the sample.

### Limitations of the study

The findings from this study suggest that VR may be useful in relieving the pain and anticipatory anxiety associated with pediatric wound care for burns. However, a further study with a larger sample size is needed. Moreover, when the children were recruited for the study, they were already on either the third or fifth change of dressing and would have developed anticipated fear. This anticipated anxiety could become a conditioning factor that would have caused their pain to escalate. Hence, the children should have been recruited at the state of their first experience with having their dressings changed. However, the objective of the study was to discern the effect of VR on pediatric pain relief from burn vis-à-vis the procedure of changing the dressings, hence, the focus was still on pain relief but perhaps on a different degree of pain. And even if children were recruited who were to have their first experience with getting their dressings changed, given the randomization of the intervention, some children would still have had been assigned to the controlled condition followed by the experimental one, which would have created more anxiety in terms of anticipated fear and pain compared with those experienced by the experimental group.

There might have been an advantage to using one nurse rather than a number of nurses, but the idea was to solicit the views of a number of nurses on the usability of the VR equipment and their possible interference with the dressing change procedure. But consistency was maintained in having the same nurse for a particular child in both the control and the experimental conditions. Hence, during the interviews, it was possible for them to report on the children's anxiety and pain before, during and after the wound care procedure in both conditions. Moreover, to ensure reliability, each nurse was given the same instructions and questions to answer by a research nurse. It would be preferable to have children with wounds located on their lower extremities, rather than on their head or dominant hand, to use this prototype.

### Clinical implications of the virtual reality equipment

A couple of nurses appeared to consider the prototype VR game that was used to be cumbersome because of the number of wires attached to the mouse, to the computer and to the eyeglasses. However, this issue could be rectified by the use of a mouse with a remote trigger. The size of the computer

machine, except to one nurse, was a non-issue since more space was available in the hydrotherapy room. But the computer could also easily be changed to a laptop if space is an issue. With regard to the nurses' satisfaction with the efficiency of the VR intervention in easing the dressing change procedure, some nurses commented that it caused them more time in terms of preparation, while others said that almost the same amount of time was involved. One nurse stated that the time taken for her to coax the child to cooperate was now replaced by the time required to teach the child how to play the game and to allow him/her time to play the game. Another two nurses said they found that the overall efficiency of the wound dressing procedure had actually increased because, in the control situation, some of the children would kick and scream, making the process very difficult. In the experimental condition, many of these children were also more relaxed and cooperative that the nurse did not have to spend as much time consoling during and after the procedure. Similar to Das *et al.*'s study (2005), in the experimental condition, the communication between the nurse and the patient was not affected.

### Conclusion and future directions

To the knowledge of the research team, this is the first randomized clinical trial in Asia on the effect of VR on pediatric burn pain when changing dressings. The preliminary findings suggest the importance of VR for controlling pain before, during and after the wound-care procedure for pediatric burn patients in Taiwan. But what seems to have set this study apart from those of the overseas is the identification of the nature of the children's responses to pain with the VR prototype. There seems to be a difference in the nature of presence and distraction. The VR intervention, which may facilitate an increase in the amount of attention drawn into the VE with both immersion and involvement (presence) is more effective in pediatric burn pain than simple distraction alone. Moreover, a decrease in anxiety experienced after the dressing change with VR intervention was observed. The timing of using the VR intervention before the child develops anxiety and pain in anticipation of the procedure would be significant.

Stemming from the preliminary results, the following venues of future research are proposed:

1. Investigate further into the exact mechanisms by which VR assists in pain modulation;
2. Include the use of biomedical assessment tool to enhance the understanding of VR for pediatric pain relief;
3. Measure the effectiveness of our prototype with repeated use since there have been many multi-participant studies

of VR today that have reported on the use of VR for pain relief for a single trial. In particular, an examination of the impact of VR on relieving pain and anxiety that the children feel after the procedure for their subsequent behaviour upon wound care;

4. Conduct larger controlled trials to elucidate the clinical efficacy of VR in the development of clinical protocols for managing pediatric burn pain and to explore a decreased use of analgesia in the presence of VR thus avoiding the side effects associated with medication.

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## Contributions

Study designs: EAC, JWYC, TKS; data collection: ASYL, JYY; analysis: EAC, JWYC and manuscript preparation: EAC, JWYC.

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