JRMO Research Protocol for Interventional Studies

Full Title	***Virtual reality as a distraction technique for the management of acute pain and anxiety during manual vacuum aspiration for miscarriage***
Short Title	*Virtual Reality in Manual Vacuum Aspiration*
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1. Contents

2. Glossary

MVA	Manual vacuum aspiration
SMM	Surgical management of miscarriage
VR	Virtual Reality

KEYWORDS

Distraction techniques

Acute pain

Anxiety

Manual vacuum aspiration

Virtual reality

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

Chief Investigator Name: _____

Signature: _____

Date: _____

4. Summary and synopsis

Short title	*Virtual Reality in Manual Vacuum Aspiration*
Methodology	*Prospective feasibility study*
Research sites	*Whipps Cross Hospital, Barts Health NHS Trust* *North Middlesex University Hospital NHS Trust*
Objectives / aims	*To study the feasibility of using virtual reality as a distraction technique for the management of acute pain and anxiety during manual vacuum aspiration for miscarriage*
Number of participants	*30*
Inclusion and exclusion criteria	*Women aged 18-50 undergoing manual vacuum aspiration*
Statistical methodology and analysis (if applicable)	*Qualitative and quantitative data analysis* ● *Patient questionnaire* ● *Staff questionnaire* ● *Semi-structured patient interview.*
Study duration	*6 months*

5. Introduction

5.1 Background

Many simple gynaecological procedures can be performed in an outpatient setting without the need for general anaesthesia. Such office-based procedures include outpatient hysteroscopy, endometrial biopsy, large-loop-excision of the transformation zone and manual vacuum aspiration for the management of miscarriage. Advantages experienced by patients include reduced anaesthetic risk, enhanced recovery time and flexibility of timings. For the healthcare provider there are significant cost benefits on the basis of reduced theatre time, staff and equipment. Patient satisfaction is generally high but influenced by their experience of pain and feelings of anxiety before, during and after the procedure.

5.2 Preclinical data

Approximately one in four pregnancies end in miscarriage with early pregnancy loss accounting for 50,000 hospital admissions a year [1]. Treatment options include expectant, medical and surgical management with patient preference and clinical suitability the key determinants. The standard option for surgical management of miscarriage (SMM) involves suction curettage under general anaesthesia. In keeping with guidance from the National Institute of Health and Care Excellence (NICE) many hospitals now also offer manual vacuum aspiration (MVA) using a handheld syringe under local anaesthesia as a safe and efficacious alternative [1]. Although there are no national guidelines as to those patients suitable for MVA the widely accepted consensus excludes women who are haemodynamically unstable, those with bleeding disorders and uterine malformations and those with retained products of conception greater than 5cm or signs of infection [2]. As with SMM, risks include uterine and cervical injury, pelvic infection, incomplete evacuation and uterine perforation. However, as most practitioners carry out the procedure under ultrasound guidance, the safety profile with regards to perforation and need for repeat procedure are favourable [2].

Like many office gynaecology procedures, MVA involves the insertion of a speculum, a degree of cervical dilatation and subsequent uterine intervention and therefore has the potential to act as a noxious stimulus at the levels of the vulva, vagina, cervix and uterus. Innervation of the uterine body is by sympathetic fibres arising from T10-L1 spinal segments, which course through the uterosacral ligaments via the inferior hypogastric nerve and ovarian plexus. The lower uterine segment, cervix and upper vagina are innervated by parasympathetic fibres arising from S2-4 whilst the pudendal nerve arising from S2-4 innervates the lower vagina and vulva.

One of the biggest challenges to patient acceptability of MVA is adequate pain relief during and after the procedure. The degree of pain experienced varies considerably from no pain to significant pain [2]. A woman's anxiety level strongly influences her perception of pain and at the time of miscarriage most women will experience a period of intense emotional distress. Comfort can be improved by the use of a suitable procedure room; kind, empathetic staff and clear

counselling with regards to what to expect during and post procedure. However, there is a paucity of data on interventions to reduce anxiety during MVA.

In the absence of general anaesthesia, pain management options include sedation, oral analgesics and paracervical block with local anaesthetic. Intravenous sedation is not a practical method for office gynaecology procedures, as it requires the presence of an anaesthetist for its administration and subsequent airway support. Non-steroidal-anti-inflammatory medications are effective in reduction of uterine contraction by the inhibition of cycloxeganse and reduction in circulating prostaglandins and patients undergoing MVA are recommended to take 400mg Ibuprofen 30-60 minutes prior to procedure [2].Whilst many outpatient gynaecology procedures are performed following administration of a paracervical block, the infiltration will not reach the level of the uterine fundus supplied by spinal nerves T10-L1. Furthermore, a Cochrane review by Tangsirwatthana *et al* 2013 concluded that there was a lack of evidence to support the use of paracervical block for cervical dilatation and uterine intervention [3].

5.3 Clinical data

Non-pharmacological methods of pain relief include distraction techniques. These may be passive; ie, listening to music, watching television or active; i.e. interactive toys, guided relaxation and controlled breathing. Intraoperative pain and anxiety ratings have been noted to be lower by use of simple intraoperative distraction techniques e.g. interacting with nurses, watching DVDs or using stress balls [4]. There is however, limited and conflicting evidence for the use of distraction techniques in office gynaecology.

A study by Angioli *et al* 2014, showed a significant reduction in pain and anxiety in outpatient hysteroscopy with the use of music however, a subsequent randomised controlled trial by Mak *et al*, 2017 showed no positive effect of music on patient's level of pain, anxiety or satisfaction at outpatient hysteroscopy or colposcopy [5,6]. Baser *et al* 2013, demonstrated women with high level pre-procedural anxiety to be more likely to perceive higher levels of pain and discomfort during colposcopy [7]. Simple visual distraction during colposcopy has been associated with a reduction in pain score but no change in anxiety levels [8].

Virtual reality is a relatively new intervention, which has been utilised as a non-pharmacological method for pain relief in paediatrics, dentistry, the management of chronic pain and the treatment of burns victims [9]. It acts as a distraction technique by giving an immersive and engaging experience, which changes the activity of the body's pain modulation system. VR distraction has been associated with significant increases in pain threshold and pain tolerance and significant decreases in pain intensity, time spent thinking about pain and self-reported anxiety relative to baseline [10]. A recent meta-analysis by Mallari *et al*, 2019, supported VR as an effective treatment for reducing acute pain [10]. A pilot study by Deo *et al*, 2019, showed promising results for the feasibility of immersive VR in outpatient hysteroscopy in reduction of pain and anxiety scores [11].

Pain management in ambulatory procedures should be multimodal and include both pharmacological and non-pharmacological interventions. Giving patients a range of options will increase the number of successful procedures and improve patient experience.

5.4 Rationale

To study the role of distraction techniques and the feasibility of using virtual reality for the management of acute pain and anxiety experienced by patients undergoing manual vacuum aspiration.

5.5 Risks / benefits

Potential benefits to participants in the study include reduction in perceived pain, reduction in anxiety and increased tolerability of procedure. Potential risks to participants include disorientation, nausea and a sensation of motion sickness. In those with a history of epilepsy it may induce seizures [12].

6. Study objectives

6.1 Primary objective

- Feasibility of using virtual reality as a distraction technique in management of acute pain and anxiety in patients undergoing manual vacuum aspiration for miscarriage.

6.2 Secondary objectives

- Understanding the acceptability and effectiveness of VR interventions in office gynaecology procedures
- Understanding the factors that might influence the willingness of patients to participate in a future formal trial of the technology.
- Understanding how best to implement the technology and designing of the contents of the VR intervention.

6.3 Primary endpoint

- Feasibility of using virtual reality as a distraction technique in management of acute pain and anxiety in patients undergoing manual vacuum aspiration for miscarriage.
- Recruitment and data analysis of 30 patients

6.4 Secondary endpoint

Qualitative and quantitative data from 30 patients in the form of

i. Patient questionnaire
ii. Staff questionnaire
iii. Semi-structured patient interview (from VR group only)

7. Study population

Participants will be recruited for the study at the Gynaecology Departments at Whipps Cross University Hospital, Barts Health NHS Trust and *North Middlesex University Hospital NHS Trust* over a 6 month period. The patients will be identified from the early pregnancy unit by the clinicians who schedule them for MVA procedure. All patients undergoing MVA that fit the eligibility criteria will be invited to participate at the time of booking the procedure. The study will recruit 30 patients.

7.1 Inclusion criteria

Patients: Clinical indications for undergoing an MVA will be confirmed.

Inclusion criteria will include all women of 18 – 50 years of age, planned for a MVA who are able and willing to give informed consent.

Staff: Inclusion criteria will include the clinician performing the MVA and the nurse supporting the clinic.

7.2 Exclusion criteria

Patients:

- Hearing impairments and blindness
- History of epilepsy or any previous seizures
- History of claustrophobia
- Any known anatomical characteristics that may make performing the office procedure more difficult (e.g., cervical conisation)
- Any known characteristics that make the patient unsuitable for undergoing MVA (e.g. known bleeding disorder, gestation >12 weeks)
- The denial or withdrawal of informed consent

Staff: The denial or withdrawal of informed consent

8. Study design

The study is a prospective trial involving mixed methods of qualitative and quantitative analysis. The study will include 30 patients attending for MVA who will be offered inclusion in the study at the time of booking the procedure.

They will be given a study information sheet, an invitation to participate with a reply slip to indicate whether they would like to participate in the study. Patients will be given standard pre-procedural information about the procedure as per standard practice. Written informed consent will be obtained from participants and the interview outputs will be anonymised.

All patients will fill in a questionnaire before and after the procedure and the 15 patients who use the virtual reality headset will have a semi-structured interview regarding their experience. This will be audio recorded. The interview will last approximately 10 minutes.

The staff in the clinic will include a clinician performing the procedure and a staff nurse supporting the clinic to whom both will be given a study information sheet regarding the study and a written informed consent for a questionnaire will be obtained from them if they agree to participate. The clinician performing the procedure will fill in a questionnaire per patient regarding the ease of the procedure and perceived pain levels of the patient. The Clinician performing the procedure and nursing staff's perception regarding feasibility of using the VR equipment for each patient who had the intervention will also be assessed through the questionnaire.

Patient follow up will not be routinely arranged for the purpose of the study. Routine follow up as per clinical requirements will be arranged as routine for the procedure performed.

9. Study procedures

The study will recruit 30 patients to use VR during MVA. On confirmation of consent the patients will be allocated to VR intervention group or no intervention standard care for MVA control group. 15 patients will be recruited to each group across both sites. Allocation to control or intervention will be performed by computer-generated randomisation. All patients will receive the same analgesia as per standard MVA protocol using para-cervical block.

The VR intervention will involve watching a standard content of the video on a mobile device using a VR headset to distract them during the procedure. The duration of the video will be 15 minutes; but the video will only be played for the duration of the MVA. Patients are allowed to stop viewing the video if they so desire and this will be recorded. If the MVA lasts longer than the VR experience the programme can be restarted and watched again.

Patients in both groups will fill pre and post procedural questionnaires. Pain and anxiety scores prior to and after the procedure will be evaluated. Scores will be measured by a Numeric Rating Scale (NRS) which is a validated measure of pain which is easy to use, has high compliance rates and detects meaningful changes in pain [13].

A semi-structured interview will be conducted with the VR intervention group patients each lasting approximately 10 minutes. The semi-structured interviews will allow for participants to be asked similar questions within a flexible framework [14,15]. The interviews will be conducted within 30 minutes of the procedure, in a suitable location and will be recorded on a digital voice recorder. The questions will be focused on the women's experiences of the procedure, their pain perception, anxiety levels and questions around the VR intervention as well as any other aspect of their hospital care they felt to be relevant. If further clarification or exploration of any particular aspect of their care was required, the interview will readdress these topics before the end of the interview. Interviews will continue until no new information is obtained, indicating that

the theoretical saturation point has been reached [16].

Clinician and nursing staff's perception regarding feasibility of using the VR equipment will also be assessed through a questionnaire. The clinician questionnaire will also assess the ease of the procedure and perceived pain scores for the patient.

Patient follow up will not be routinely arranged for the purpose of the study. Routine follow up as per clinical requirements will be arranged as routine for the procedure performed.

Patients and staff can withdraw from the study if they so desire at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care or treatment that they receive.

The study will end once the proposed numbers of patients have been recruited and data analysis completed. Participants will be debriefed after their participation in the study and will be directed to suitable support agencies if necessary.

10. Assessment and management of risk

Possible risks of participation in the study include the potential to experience the side effects of nausea, headaches and motion sickness during the use of VR programme. Approximately 25-40% of users of VR experience these symptoms. The risks are greater with prolonged use of more than 30 minutes [12]. VR is a known trigger for seizures in those with a history of epilepsy, for this reason women with any history of seizures or epilepsy will be excluded from the study.

Participants will be informed of these risks at the time of invitation to the study and details will be included in the patient information leaflet. Any participant wishing to end the VR programme may do so at anytime and this will be recorded.

11. Statistical considerations

11.1 Sample size

The study will include 30 patients with 15 patients in the VR intervention group and 15 patients in the MVA standard care control group.

○ 11.2 Method of analysis

The recruitment of women and interviewing will proceed alongside data coding and preliminary analysis.

The statistical analysis will include statistical comparison of pre and post anxiety and pain scores. Interview analysis will be performed by the chief investigator and/or study manager. Interviews will be transcribed verbatim and initially coded by reading and re reading the transcript and making notes, drawing on the observations made during the interviews and transcription. Transcripts will be coded line-by-line, describing,

summarising and attending to linguistic elements such as pronoun and metaphor use. The transcripts will be entered into a qualitative software package (N6) and a thematic analysis undertaken from the emergent themes developed from these codes and cluster with related themes. Initial coding is Initial phase, which involves open coding. Axial coding and selective coding with use of constant comparison will enable a cyclical and iterative process on the principles of grounded theory. Analytic frame for the analysis will be linked to the primary and secondary aims.

Staff questionnaires will be analysed to correlate pain scores of actual vs. perceived and feasibility of carrying out the intervention will be assessed.

Demographic data would include age, parity and ethnicity.

Data and all appropriate documentation will be stored for a minimum of 20 years after the completion of the study, including the follow-up period.

12. Ethics

The Chief Investigator will obtain approval from an NHS ethics committee. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so will be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

Conflicts of interest
The CI and PI have no conflicts of interest.

13. Public Involvement

The inspiration for this study was a patient's inquiry about using her own VR headset during MVA. They subsequently aided in the study design, choosing of video content and the VR device. Informal feedback from patients offered the VR device during MVA procedure include "good distraction"; "visual nature goggles helped so I didn't watch or listen" and "wouldn't want to see the procedure".

14. Data handling and record keeping

14.1 Data management

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

14.2 Source data

Source data will be in the form of patient demographic data, questionnaire and interview responses. This information will be managed in accordance with the Data Protection Act, the General Data Protection Regulation (GDPR), NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research, and the conditions of Research Ethics Committee favourable opinion.

14.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, the General Data Protection Regulation (GDPR), NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research, and the conditions of Research Ethics Committee favourable opinion.

14.4 Record Retention and Archiving

When the research trial is complete, the records are kept for a further 20 years. The approved repository for long-term storage of local records is the Trust Corporate Records Centre

15. Interventions and tools

15.1 Devices

Oculus Go virtual reality headset which will display a 15 minute VR video.

15.2 Tools

- Numeric Rating Scale (NRS) is a validated measure of pain, which is easy to use, has high compliance rates and detects meaningful changes in pain. The NRS is an 11-point scale consisting of integers from 0 through 10; 0 representing ‘‘No pain’’ and 10 representing ‘‘worst imaginable pain.’’ Respondents select the single number that best represents their pain intensity. Ratings of pre-operative anxiety are measured by an 11-point numeric rating scale. ‘How would you rate any anxiety you may currently be feeling’ 0 (no anxiety) and 10 (worst anxiety imaginable) [13].
- Semi structured interviews will allow for all participants to be asked similar question within a flexible framework [14,15].

16. Safety reporting

16.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences, which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

16.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression ‘reasonable causal relationship’ means in general that there is evidence or an argument to suggest a causal relationship.

16.3 Notification and reporting of Adverse Events and Reactions

If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants’ source documents, the Case Report Form (CRF), and, where appropriate, medical records.

16.4 Serious Adverse Events (SAEs) or reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,

- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

SARs will be reported to the REC where in the opinion of the Chief Investigator the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

16.5 Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

16.6 Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However the CI will inform the sponsor and Research Ethics Committee (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

16.7 Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

16.8 Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

17. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

On site monitoring will be performed as per the study monitoring plan. Monitoring will include source data verification.

18. Trial committees

The study management group will consist of the Chief Investigator and Principal Investigator.

The study may be subject to inspection and audit by Barts Health NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

The day-to-day management of the study will be co-ordinated through Dr Anna McDougall, Specialist Registrar in Obstetrics and Gynaecology and PI for the study.

19. Finance and funding

Barts Health NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

There is no funding for this study.

20. Indemnity

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

21. Dissemination of research findings

On completion of the study, the findings will be published as per Barts Health NHS Trust policy and publication of the findings will be done via peer-reviewed journals.

22. References

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