Targeted perfusion based haemodynamic management in critically ill patients using urethral perfusion – a pilot study.

Short Title: TARGET – UP

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1. Background and rationale

Ensuring adequate blood flow and delivery of oxygen and substrate to cells, tissues and organs is a key facet in the management of the critically ill patient, irrespective of the aetiology of the underlying disease. Patients with inadequate tissue perfusion, whether from sepsis, cardiogenic failure or haemorrhage have demonstrably worse clinical outcomes. Despite this, accurate quantification of tissue perfusion in the critically ill remains challenging. One reason for this is the lack of coherence between blood flow in the large blood vessels and heart and that within the smaller blood vessels that provide the final pathway for oxygen and substrate delivery. This haemodynamic incoherence can lead to patients being classified as fluid responders, based on an increase in stroke volume in response to fluid, when in fact, such fluid does not result in an increase in tissue perfusion. Given that both excess fluid administration in the critically ill and failure to improve tissue perfusion leads to worse clinical outcomes it is important to take a targeted approach to treatment. A point of care device that has utility to detect changes in perfusion at the level of the tissues, rather than the central circulation would allow more effective treatment of shocked and critically ill patients.

Plethysmography uses the principal of differential absorbtion of infra-red light between blood and tissues in order to produce a value reflective of changes of blood volume within a target tissue. The plethysmographic signal return is comprised of two components, pulsatile and non-pulsatile; comparing the relative strengths of the pulsatile component to the non- pulsatile component produces a value termed the Perfusion Index (PI). Peripheral PI, utilising finger plethysmographs, has been studied in critically ill patients but due to the peripheral vasoconstriction and blood flow diversion that often occurs in shock states, its utility is limited.

Urethral perfusion impairment is likely to occur early and become significant during shock states and thus represents a potential candidate site to assess the tissue perfusion of visceral organs. The IKORUS UP device (Vygon, France) is a modified Foley urethral catheter equipped with plethysmographic sensors and receivers. An initial feasibility study has shown the device to be both safe and reliable, producing an excellent signal quality 99% of the time. Animal experimental studies and case reports suggest that the IKORUS device is responsive to changes in the haemodynamic state caused by induced shock and vasopressor administration but further studies are required in order to prove feasibility in critically ill patients over a prolonged time course and to collect pilot data relating to the effects of fluid administration and vasopressor agents on the UPi signal in the context of other haemodynamic changes.

2. Aims

- To assess the safety and feasibility of the IKORUS UP device in critically ill patients
- To assess the response signal of the IKORUS UP device to fluid challenges in critically ill patients and to compare these responses to those seen using a monitor of macro haemodynamic blood flow. *A priori* phenotypes will be defined based on these responses and characteristics of these phenotypes explored.
- To assess the role of the IKORUS UP device in setting individualised targets for vasopressor therapy in critically ill patients.

3. Study design

3.1 Overview

Interventional pilot study

3.2 Setting

Intensive care units of participating sites

3.3 Population

Critically ill patients with any diagnosis within 24 h of ICU admission

3.3.1 Inclusion Criteria

Adult >/= 18 years of age
Within 24 h of ICU admission
Predicted length of ICU stay at least 5 days
Receiving >0.1 mcg/kg/min of noradrenaline at time of study enrolment

3.2.2 Exclusion criteria

Palliative treatment intent
Contra indication to urethral catheterisation or complication during previous urethral catheter insertion
Contraindication to fluid or vasopressor challenges in the opinion of the attending clinician

3.2.3 Co-enrolment

Co-enrolment will be considered by the PI into other interventional studies where there is no possible conflict with the TARGET-UP study objectives. Co- enrolment agreements will be put in place on a case-by-case basis. Co-enrolment will be permitted with studies that do not involve an intervention (e.g. observational studies).

3.2.4 Screening

Daily screening will take place and details of eligible patients will be entered into a screening log. Eligible patients will be identified by attending clinical staff and notified to the research team. Reasons for non-recruitment of eligible patients will be recorded in the screening log.

3.3 Recruitment and consent

3.3.1 Overview & rationale

Patients, eligible for inclusion in the study are critically unwell, invariably receiving sedative medications, organ support and exhibiting both a reduced level of consciousness and inability to effectively communicate. For all these reasons they lack capacity to provide prior informed consent. The point of maximal scientific interest and potential for future treatment developments occur primarily in the first hours and days of critical illness during this period of mental incapacity. These factors, alongside the potential distress of the emergency situation and the primacy of clinical discussions, makes any attempt to obtain either prior informed consent from the patient, or the opinion of their Personal Consultee (i.e. relative or close friend), prior to commencement of the study protocol inappropriate.

For these reasons once an eligible patient has been identified who fulfils the inclusion criteria they will be entered into the study after taking advice from the referring clinician, acting as a nominated consultee. Subsequent opinion will be sought from a friend or relative (personal consultee) and ultimately consent for use of data will be sought from the patient after they regain capacity.

3.3.2 Role of Nominated Consultee

The clinician referring the patient will also assume the role of nominated consultee. This individual will not be a member of the research team. The role of the nominated consultee will be to express an opinion as to whether the patient is suitable for inclusion in the study. They will receive information relating to the nature of the study in the form of an information sheet. Nominated consultees will be asked to indicate agreement for enrolment in the study.

3.3.3 Role of Personal Consultee

As outlined in Section 3.3.1 it will not be possible to involve trial participants in the consenting process at study recruitment. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into the study, a delegated member of the research team will approach a close friend or relative, known as a personal consultee, as soon as appropriate and practically possible to discuss the trial and to seek advice as to the patients' likely wishes and feelings regarding participating in research. Ideally, this approach would take place within 24-48 hours of study enrolment, once the patient's medical situation is no longer an emergency and initial meetings between the consultee and treating clinicians have occurred.

The Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented by information about why the Personal Consultee has been approached at this stage. A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in research. Personal Consultees will also be asked to indicate on the Personal Consultee Opinion Form whether, in their opinion, the patient would agree to access to medical records for data collection.

Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients' participation in the study. After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the person seeking opinion will invite the Personal Consultee to sign the Personal Consultee Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient's medical notes and the original kept in the Site File.
If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in research, then no further data collection will occur.

3.3.4 Informed consent from participants

Following enrolment, patients will be approached once they have been deemed to have full capacity to provide informed consent. At this stage study interventions will probably have concluded and

consent will be related to the use of collected data. A Participant Information Sheet (PIS) will be provided to the patient. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to physical incapacity), an independent witness can sign on their behalf.

3.3.5 Event of patient death

In the situation where the patient dies any data collected will be used in analysis. There will be no requirement to make further approaches to a consultee in this instance.

3.3.6 Event of discharge / transfer prior to recovery of capacity

In the rare situation where the patient is transferred to another hospital prior to consent being sought, then the most appropriate member of the site research team will liaise with the receiving hospital to establish at which point capacity has been regained and when discharge is probable. If possible, patients will be approached by researchers in person at the other site to provide informed consent for data use. Patients will not be contacted remotely (e.g. by letter).

3.4 Procedures

3.4.1 Overview and timepoints

Each enrolled patient will undergo a series of fluid and vasopressor challenges at three time points. The precise timing of the fluid and vasopressor challenges will depend on investigator availability and the time windows are deliberately broad.

Early: At study enrolment; within 24 h of ICU admission
Mid: 48-72 h after ICU admission
Late: 96-120 h after ICU admission

Fluid challenges will be delivered first followed by the vasopressor challenge.

3.4.1 Fluid Challenge

A fluid challenge (FC) is defined as a 250ml bolus of a crystalloid solution, which will usually be Hartmann's solution or 0.9% saline. This will be administered at as rapid a rate as possible through existing vascular access devices, preferably a central venous catheter.

A focussed transthoracic echo will be performed immediately before the FC. A five chamber view will be obtained and the left ventricular outflow tract visualised. The LVOT VTi signal will be assessed using gated PW Doppler. Immediately following the FC, the LVOT VTi will be measured again. The patient will be classified as a SV responder if the VTi increases by > 10%

The IKORUS UPi signal will be recorded immediately prior to, and immediately after the FC. The patient will be classified as a UPi responder if there is an increase in the UPi signal of > 10%

3.4.2 Vasopressor Challenge

Vasopressor challenges will be conducted only in patients who are already receiving noradrenaline. A vasopressor challenge will consist of sequentially increasing the dose of noradrenaline to serially target mean arterial pressures of 60,65,70,75 & 80 mmHg. MAP will be maintained at each stage for 5 minutes. The mean UPi signal over the 5 minute period will be used as the dependent variable.

Following the vasopressor challenge the MAP target will return to that mandated by the attending clinical team.

As close as possible to the time of the fluid and vasopressor challenges, the following additional procedures will be performed:

Paired arterial and venous blood gas measurements
Capillary refill time measured using a standardized technique
Sublingual incident dark field video-microscopy
Point of care ultrasound to measure VEXUS score

3.5 Outcome measures

3.5.1 Safety and Feasibility

- Complication rate related to insertion of IKORUS catheter (bleeding, failure to insert)
- Relative amount of time that the IKORUS catheter returned a good quality UPi signal (defined as > 65%).

3.5.2 Quantification and Characteristics of Fluid Response Phenotypes

- At each intervention timepoint patients will be characterised in one of 4 phenotypes depending on their response to a fluid challenge. A responder will be classified as having a > 10% increase in the selected variable (SV or UPi):
    - Phenotype 1 SV responder, UP responder
    - Phenotype 2 SV responder, UP non responder
    - Phenotype 3 SV non responder, UP responder
    - Phenotype 4 SV non responder, UP non responder
- Timepoints will be classified as Early D0/1, Mid D2/3, Late D4/5
- The following characteristics of these phenotypes will be reported:
    - HR, BP, inotropic support
    - Fluid balance (Immediate, 24h and LOS)
    - CRT
    - Peripheral plethysmographic perfusion index
    - Lactate / ScvO2 / delta CO2
    - IDF parameters (TVD, PVD, MFI, MHI)
    - VEXUS score

3.6 Data collection

This trial will be coordinated from the ACET research team at KCH. Data will be collected by local investigators. Only data as set out on the CRF will be collected for this study.

3.7 Data management

All participant data collected will be entered onto a paper CRF before being transferred to an electronic spreadsheet. The PI will oversee and be responsible for data collection, quality and recording.

Security of the electronic spreadsheet is through restricted access permissions. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act.

3.8 Device Information

The device used in the study is called IKORUS UP and is manufactured by Vygon (Ecouen, France). The device is CE marked and is being used within its intended purpose. The monitoring system consists of a base unit and disposable urethral catheters with an integrated plethysmographic sensor. The urinary catheters are single use (disposable) but can be left in situ indefinitely. The urinary catheters will be purchased but the base unit will be on loan from the manufacturer for the duration of the study. Training on the use of the device has been provided by the manufacturer to the research team.

4 Safety Monitoring & Reporting

4.1 Definitions

Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence affecting a trial participant during the course of a clinical trial which does not necessarily have a causal relationship with the study. It should be noted that all eligible study patients are by definition critically unwell with the propensity to develop multiple adverse events during the course of the study.

Adverse Device Event (ADE)

All untoward and unintended responses to a medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is an adverse event that:

· Results in death
· Is a life-threatening situation
· Requires prolongation of hospitalisation
· Results in persistent or significant disability or incapacity

Serious Advice Device Events (SADE)

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device, which resulted in any of the characteristics or led to characteristics of a Serious adverse event.

SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances has been less opportune.

All cases are to be assessed by either the reporting medically qualified professional or the sponsor.

Relatedness

None: there is no evidence of any relationship to the study treatment or device

Unlikely: there is little evidence to suggest a relationship to the study treatment or device, and there is another reasonable explanation of the event

Possibly: there is some evidence to suggest a relationship to the study treatment or device, although the influence of other factors may have contributed to the event

Probably: there is probable evidence to suggest a relationship to the study treatment or device, and the influence of other factors is unlikely

Definitely: there is clear evidence to suggest a relationship to the study treatment or device, and other possible contributing factors can be ruled out.

Expectedness

Expected adverse device events: The follow events are defined as expected ADEs and are related to potential complications of urethral catheterisation.

- Haematuria
- New urinary sepsis – confirmed by urinary bacteriological culture
- Urethral trauma during catheter insertion or removal

Unexpected adverse device events (UADE) : Other events not listed above that are causally related to the IKORUS UP device.

4.2 Recording and reporting AEs

All SAE/SADE/UADEs need to be reported to the sponsor/legal representative, manufacturer, and R&I within one working day of the research team becoming aware of them.

Reports of related and unexpected SAEs should be submitted to the REC within 15 days of the Chief Investigator becoming aware of the event, using the SAE/SADE report form

All reporting to King's College Hospital NHS Foundation Trust should be by e-mail giving as much information about the incident as possible, and should be signed by the PI or Co-investigator. The SADE reporting form should be used for King's College Hospital NHS Foundation Trust sponsored studies.

The sponsor will undertake an initial review of the information and ensure it is reviewed by the MEMS. Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner.

Reporting to the MHRA will be done in liaison with the Chief Investigator and the Manufacturer.

The Manufacturer has a legal obligation to report all events that need to be reported to the Nominated Competent Authority immediately (without any unjustifiable delay) after a link is established between the event and the device, but no more than:

- 2 days following the awareness of the event for Serious Public Health Threat.
- 10 days following awareness of the event for Death or unanticipated serious deterioration in health.
- 30 days following the awareness of the event for all other event meeting the SAE criteria.

4.3 Serious Adverse Events that do not need reporting

Patients recruited to the TARGET UP study are by definition critically unwell and by definition meet the criteria for SAE reporting on a frequent basis. SAEs will only therefore be reported if there is a casual link to the study, in the opinion of the investigator or attending staff, or if the frequency and / or nature of the pattern of SAE is, in the opinion of the investigator or attending clinicians, out of keeping with the expected pattern of illness.

5. Study closure

5.1 Data archiving

Data will be archived for 3 years after study closure.

6. Statistics and data analysis

All images will be assessed offline by a single operator.

6.1 Sample size

This is a pilot study with exploratory outcomes and a power calculation is not appropriate. A pragmatic sample size of 30 patients has been selected based on the feasibility of ease of recruitment.

6.2 Statistical Analysis

Feasibility data will be reported without further analysis.

Differences in variables based on fluid challenge phenotypes will be assessed using appropriate statistical tests based on distribution of data.

For vasopressor challenges the following data analysis will be performed:

- Overall uPi at each MAP target for the entire cohort
- delta uPi at each MAP target above 60mmHg
- For each individual patient the MAP inflection point (defined as the MAP target at which the greatest uPI signal was recorded)

7. Ethical compliance and standards

The TARGET UP study will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the Data Protection Act (1998) and the Mental Capacity Act (2005).

7.1 Study registration

The study will be registered with an appropriate clinical trial registry prior to commencement.

7.2 Central ethical compliance

The study will be reviewed by a REC through the normal IRAS process

The PI will submit annual progress reports and all protocol amendments to the REC for review.

8. Data handling and management

The study complies with the principles of the Data Protection Act, 2018. At all times researchers will act to preserve the confidentiality of patient identifiable data.

Patients will be de-identified by allocation of a unique study number and collected data will be referred to this study number rather than to personal identifiable information. Personal data, including full name, contact details, date of birth and NHS number will be required to successfully follow-up enrolled patients and will be linked to collected data on a separate electronic spreadsheet. Only members of the immediate research team will have access to personal identifiable data. Personal data will not be retained after follow up is complete and will be deleted at this time. The research team will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified.

All physical data, such as Clinical Report Forms & Consent Forms will be securely stored in a site file within a secure research office.

All electronic data will be maintained on a secure electronic database accessible only by members of the research team.

9. Sponsorship and Funding

9.1 Sponsoring Organisation

The study is sponsored by King's College Hospital NHS Foundation Trust.

10.2 Funder

The study is funded by the Medical Directorate of the Defence Medical Services, part of the UK Ministry of Defence and by a grant awarded by the European Society of Anesthesiology and Critical Care.

10. Dissemination of results

The results of the TARGET UP study will be widely and actively disseminated through publication in peer reviewed medical journals and presentations at national and international meetings.

11. Peer and regulatory review

The study has been peer reviewed in accordance with the requirements outlined by the Sponsor. The Sponsor considers the procedure for obtaining funding from the Research Directorate of the Defence Medical Services and the award of a competitive grant from the European Society of Anesthesiology and critical care to be of sufficient rigour and independence to be considered an adequate peer review.

The study was considered and received a favourable opinion from the XX Research Ethics Committee (INSERT REC REF)

12. Indemnity Arrangements

King's College Hospital will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office.