# Standard Operating Procedure (SOP)

# Management of intervention group patients

# SOP 001

Authors: Mark Edwards & Rupert Pearse

Authorisation: Rupert Pearse (Chief Investigator)

## Scope

- To provide guidance on management of patients who have been allocated to the intervention group in the OPTIMISE II Trial.
- The procedures for administering the intervention are described in detail below and a summary is provided on page 5.

## Procedure

- The trial intervention period will commence at the start of general anaesthesia and continue for four hours after surgery is complete (maximum total duration: 24 hours).

## Cardiac output monitoring

- Investigators may only use commercially available cardiac output monitoring equipment provided by Edwards Lifesciences in this trial. This will consist of the EV1000 monitor, with either the non-invasive ClearSight or the arterial catheter based FloTrac device.
- Immediately following induction of anaesthesia, the selected Edwards Lifesciences system will be set up for monitoring of cardiac output.
- Delays in setting up cardiac output monitoring should be avoided. If monitoring has been used for less than 80% of the intervention period this meets the definition of a protocol deviation and should be reported as such.

## General haemodynamic measures

Care for all patients has been loosely defined to avoid extremes of clinical practice but also practice misalignment, as follows:

- Patients will receive 5% dextrose at 1 ml/kg/hr as maintenance fluid.
- Additional fluid will be administered at the clinician's discretion, guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base deficit.
- Blood will be transfused to maintain haemoglobin at greater than 8 g/dl.
- Oxygenation will be maintained at $Sp0_2$ 94% or greater.
- Heart rate will be maintained at less than 100 beats per minute.
- Core temperature will be maintained at 37°C.
- Mean arterial pressure will be maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilator as required, although other measures such as adjustments to anaesthesia and analgesia should be considered first.

## Post-operative analgesia and sedation

- Post-operative analgesia will be provided at the discretion of the clinician in accordance with local protocols. This may include epidural infusion (bupivicaine and fentanyl), intrathecal opioids (fentanyl, morphine, diamorphine), wound catheter infusion (bupivacaine), opioid-based patient-controlled analgesia system, oral analgesics (including opioids) or intra-venous infusion (opioids or lidocaine).
- If required, post-operative sedation will be provided with propofol or midazolam.

## Plasma potassium and glucose monitoring

- Monitoring of plasma potassium and glucose levels is recommended.

## Administering fluid to a stroke volume end-point

- Currently, peri-operative intra-venous fluid is usually administered to subjective end-points. The use of stroke volume as a treatment end-point may significantly reduce but not eliminate this subjectivity. However, the measurement of stroke volume does not replace the discretion of the treating clinician in ensuring patient safety. The protocol allows for the treating clinician to adjust both the volume and type of fluid administered, e.g. if there is concern about persistent

hypovolaemia or fluid overload. Such decisions may relate to clinical circumstances or physiological measurements (e.g. pulse rate, arterial pressure, urine output, serum lactate, base excess).

- Stroke volume will be determined by the cardiac output monitoring system. In order to ensure a standardised approach to fluid administration, no more than 500ml of intra-venous fluid will be administered prior to commencing cardiac output monitoring.

- Patients will receive 250ml fluid challenges, within duration of five minutes, with one of the following solutions, aiming to maximise stroke volume:
    - "Balanced" crystalloid: Hartmann's solution (compound sodium lactate, Ringer's lactate), Plasmalyte 148.
    - 0.9% sodium chloride
    - Gelatin-based colloid
    - Starch-based colloid
    - Albumin

- Maximal stroke volume is defined as the absence of a rise in stroke volume of at least 10% sustained for 20 minutes or more in response to a fluid challenge. Thus in the absence of such a rise in stroke volume, further fluid challenges are unlikely to be helpful at that time.

- Once the maximal value of stroke volume is determined, this should be maintained throughout the intervention period with fluid boluses as required. Initial increases in stroke volume are often only transient. If stroke volume does not increase as defined above, it is likely that the heart is functioning on the horizontal part of the Starling curve (see figure). This suggests the patient is not hypovolaemic and fluid challenges should be stopped. If the stroke volume decreases, this is most likely due to ongoing fluid losses and a further fluid challenge is required.

- Stroke volume variation less than 5% suggests that fluid responsiveness is unlikely, so a fluid bolus is not recommended.

- Many peri-operative physiological changes may alter the maximal value of stroke volume. These may be due to general and regional anaesthesia, surgical stimulation, endotracheal tube removal, pain, fluid loss, etc. Further fluid challenges should be considered where there is reason to believe the maximal stroke volume may have changed. The most challenging situation is the

patient who clearly remains stroke volume responsive despite large volumes of intra-venous fluid. This arises when an evolving severe fluid deficit has yet to become clinically apparent in any other respect. Experience from previous trials suggests that it is particularly important to continue to give fluid challenges in such patients to maintain maximal stroke volume. The small volume of each individual fluid challenge will minimise any potential adverse effects of confirming volume status in euvolaemic patients. Data from previous studies confirm the safety of this approach.

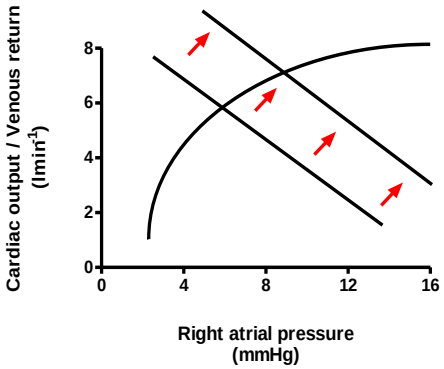


**Figure: Starling's curve**
**The increase in venous return due to intra-venous fluid (red arrows) increases stroke volume in responsive patients. At maximal stroke volume (horizontal part of curve), the absence of a response indicates fluid is not required.**

## Inotrope

- Patients in the intervention group will also receive a low dose inotrope infusion at a fixed rate which will be commenced after fluid replacement has been initiated. The choice of inotrope will be made at the discretion of the local investigator, according to local preference and availability. The options are dobutamine at a fixed dose/rate of 2.5 µg/kg/min and dopexamine at an equipotent dose/rate of 0.5 µg/kg/min. Because of the vasodilator effects of dopexamine/ dobutamine, correction of hypovolaemia (if present) should be initiated at least 30 minutes prior to commencement of the infusion. The infusion rate will be reduced and/or discontinued if the patient develops a tachycardia (heart rate greater than 100bpm) for more than 30 minutes despite adequate anaesthesia and analgesia. Data collection and follow-up for such patients will be performed as normal. All other management decisions will be taken by clinical staff.

## What if blood products or intravenous fluids are required for indications unrelated to changes in stroke volume?

- Many intervention group patients will require blood products and, in some cases, additional intravenous fluid challenges may be requested by a clinician. Administration of fluid, blood or blood products under these circumstances should be guided by stroke volume monitoring and these data should be used to inform the need for subsequent fluid challenges.

## Summary

### General haemodynamic measures

1. 5% dextrose at 1 ml/kg/hr
2. Transfuse blood to maintain haemoglobin >80 g/l
3. Clinician retains discretion to adjust therapy if concerned about risks of hypovolaemia or fluid overload
4. Mean arterial pressure 60-100 mmHg; $Sp0_2$ ≥94%; temperature 37°C; heart rate <100 bpm

### Administering fluid to a stroke volume end-point

1. 250ml fluid boluses to achieve a maximal value of stroke volume
   [*Note: Start inotrope after first fluid challenge – see below*]
2. Fluid challenges should not be continued in patients who are not fluid responsive in terms of a stroke volume increase
3. Fluid responsiveness is defined as a stroke volume increase ≥10%
4. If stroke volume decreases further fluid challenge(s) are indicated
5. Persistent stroke volume responsiveness suggests continued fluid loss
6. Fluid challenge is not recommended if stroke volume variation is <5%

### Low dose inotrope infusion

1. Start fixed rate infusion of dobutamine (2.5µg/kg/min) or dopexamine (0.5µg/kg/min) after first fluid challenge.
2. Halve dose if heart rate rises to greater than 100bpm for more than 30 minutes.
3. Stop infusion if tachycardia persists.

### What if blood or IV fluid is required regardless of stroke volume?

1. If blood products or additional fluid challenges are required, then stroke volume should still be monitored to identify any change in maximal stroke volume