



Postoperative vasopressor usage: a prospective international observational study

'SQUEEZE'

Frequently Asked Questions (FAQ)

Why are you studying postoperative vasopressor infusions (PVI) when postoperative hypotension (without vasopressor infusions) is a bigger problem?

We agree that postoperative hypotension may be difficult to evaluate clinically and is an important area of further study. However, identification of patients with postoperative vasopressor infusions is relatively simple (are they on them: yes or no?) compared to identifying patients who have had surgery and are hypotensive and there isn't a simple explanation like hypovolaemia. Excluding hypovolaemia is complex and contentious, and arguably not simple to do without advanced monitoring.

Why are you doing this study – what's the point? It's obvious that postoperative vasopressor infusions (PVI) are uncommon, but when they do occur it's in the sicker patients and therefore, they have inferior outcomes.

To some extent this is true. However, in our clinical practice patients receiving vasopressor infusions following surgery is much more common than patients with severe ARDS, or refractory septic shock, or other popular areas of research (!) and as a common problem that has never been subject to rigorous evaluation – we believe is a worthy area of study. This was supported by the findings of our micro-survey: “Non-cardiac surgery patients receive vasopressor infusions after surgery:” ‘occasionally’ in 58%, and ‘frequently’ in 22%.

Secondly, we will be able to match patients by severity of illness (and possibly by type of surgery) and compare the relative incidence of adverse events by type of vasopressor – which may inform hypotheses that can be evaluated in future studies: for example, atrial fibrillation may be far more common in patients treated with dopamine, or renal replacement in patients treated with adrenaline.

Finally, the significant variation in practice (shown in our analysis of the EuSOS data) potentially reflects uncertainty – practitioners don't have a clear idea of what represents optimal treatment. We'll be able to assess if different ways of evaluating when to start PVI influence the prevalence of PVI, for example it may be that using goal-directed fluid therapy is associated with more PVI than clinical assessment alone.



Why are you collecting so much information on those in cohort A, when only 2% of them will be of interest to you?

To determine which factors are associated with PVI we need to study a population who may or may not receive PVI. By keeping the population very broad (only excluding cardiac, obstetric, transplant and daycase surgery) we maintain good generalisability. In order to compare clinical outcomes (length of stay, morbidity and mortality) between those with and without PVI, we need to collect the clinical outcomes in both populations.

The inclusion criteria – what about day case surgery with unexpected complications?

We do not want to recruit people having minor surgery, including day case surgery. However, if a patient has surgery that is initially meant to be minor and then return home on the same day, but there is an unexpected complication and they stay in hospital for medical reasons – they are eligible and can be enrolled.

Why two cohorts? It's confusing!

The need for cohort A is described above, the second cohort (B) will allow us to have a large cohort of patients receiving PVI. We anticipate a wide range of severity of illness – with some patients only receiving a couple of hours of low dose vasopressor and some, perhaps those who had major intra-operative complications, to have prolonged high-dose and possibility multiple PVI. A definition of postoperative vasoplegia will always be arbitrary but having these data might be informative. Defining postoperative vasoplegia will help in the design of future clinical trials.

There is no rule on the order of the cohort that should start first. Centres can start recruiting to Cohort B and decide when to recruit Cohort A – as long as it is completed within 12 months after starting Cohort B recruitment.

And two CRFs!

CRF1 is for all patients. CRF2 is just for those who receive a PVI.

Please may I just recruit to cohort A? or B?

No, sorry. It wouldn't be useful data for us.



Why aren't you analysing X, or Y, or Z?

We will have a huge amount of data and there are many possible analyses. Please get in touch with the SSC as the statistical analysis plan isn't finalised yet – although it will be before the database is closed. If you'd like to lead on running a specific analysis of interest to you then please get in touch – we're highly likely to support you leading on a secondary analysis.

"I'd like every patient in my country to have a urinary biomarker of AKI, how do I do this?"... or "serial serum troponins"...

We encourage nested studies so please get in touch with the SSC and share your idea - we'll support you. If the extended study requires consumables or other additional expenses you'll need to apply for the funds, again – with our support.

Why are you asking for us to recruit so many patients in a week – it's incredibly difficult to do this!

We want to avoid the risk of introducing bias by attempting to collect data on consecutive patients, spanning a full week (Tuesday to Monday). We accept that some patients will be missed.

This study will only run successfully in hospitals that have enough suitable staff to help run the study for the week in question. If insufficient numbers of patients are recruited during this week then all the data from that centre may be discarded. We are not going to state our minimum number of recruits as experience tells us that some centres will adopt the minimum as their recruitment target – which we'd like to avoid.

ISOS and EuSOS used a similar methodology and most hospitals recruited 50-120 patients in one week.

"It's easier to do cohort A over 2 weeks – is this ok?"

Unfortunately, not. If you can only recruit a small number in a week, why? If it is because you are a small centre and will not have many eligible patients – this is ok.

If it is because it's too challenging as there are too many patients and not enough staff – then there is a solution. It's inferior to recruit 30 patients out of 300 without a system in place as there is a risk that the 30 you recruit are not representative of the 300 – i.e. you are introducing bias. It's better to use a system – please contact the ESAIC office and they will advise you on our preferred formal randomisation process.



“30 consecutive patients that receive postoperative vasopressor infusions” What if we miss one?

Once the busy week is over, we encourage all participating hospitals to screen daily to identify patients who are receiving PVI. We accept that most hospitals will not screen at weekends and therefore some are likely to be missed. However, it may be possible to screen on Monday for those who had PVI on Saturday or Sunday and collect their data. As described above – most of the information can be gained from reading the medical notes. If you’re in a high-volume hospital and would prefer to only recruit patients that you can see on the day of surgery (to determine clinical frailty scale and whether or not they took their hypotensive medications on the day of surgery) then that’s acceptable.

Do I have to collect all the data at the time of surgery?

Given that most patients will not have PVI only the first CRF will need to be completed (CRF1) and most of this can be determined from scrutinising the medical notes, and therefore doesn’t need to be done at the time of the surgery. Some aspects might be difficult to ascertain from the medical notes and are best determined close to the time of surgery: i) whether or not they took antihypertensive medications on the morning of surgery, and ii) Clinical Frailty Scale. We anticipate that all the other data for the CRF is likely to be documented in the patient’s medical records – but this may vary by healthcare environment.

For those who receive PVI, additional information is required in CRF2 but we anticipate that all of this is likely to be documented in the patient’s medical records or can be determined retrospectively.

Why aren’t you using standard endpoints like EPCO or StEP for respiratory complications?

We want to keep the burden on data collectors as low as possible. We’ve deliberately kept the case report form (CRF) as brief as possible and we’ve aimed to make it as simple as possible to complete – for example: either they did, or did not, receive invasive mechanical ventilation.

Do we have to come in at weekends to collect data?

The week that has been chosen to collect data starts on a Tuesday to allow final plans to be put into place on Monday. Recruiting patients on Saturday and Sunday is desirable but as described above, only limited data needs to be collected on the day of surgery.



It's our practice to give repeated boluses of vasopressors and we very rarely use infusions, what do we do?

That's not a problem. There is space on CRF1 to document that the patient received boluses during and after surgery as appropriate. If they received an infusion that continued more than 1 hour after the end of surgery then CRF2 should also be completed.

Why are you excluding cardiac patients? That's where all the postoperative vasopressor infusions are.

Undoubtedly patients receive PVI commonly after cardiac surgery and a study like Squeeze in this population would be very valuable. There are several factors that would complicate interpretation though: reduced cardiac output may contribute to hypotension, the cause of which must be ascertained early – differentiating between reduced preload from bleeding, impaired myocardial contractility or the occurrence of cardiac tamponade. The second main complicating factor is the frequent use of vasodilatory inotropes that directly influence vascular tone.

What about thoracic patients?

By contrast, we are happy to include thoracic surgical patients. In the protocol (page 19) thoracic surgery is not listed as an exclusion (contrary to the protocol overview on page 6 where it erroneously says that cardiothoracic patients are excluded).

In CRF2 you ask about SOFA score and maximum infusion rate – I don't have this information.

The SOFA score reflects severity of illness and is simple to calculate. If there is missing data then an approximation is acceptable – for example if bilirubin wasn't measured but there is no suspicion of liver dysfunction that it's reasonable to use the lowest possible score in that domain, similarly platelets if there are not reasons to suspect thrombocytopenia.

If a patient is receiving an infusion of vasopressor it is possible using simple arithmetic to work out the infusion rate, for example in micrograms per kilogram per minute (mcg/kg/min).

Why don't you ask where the patients are being treated in CRF2?

There is no universal definition of what is meant by "intensive care unit" or "post-anaesthetic care unit" and this limitation probably means that analyses based upon location within the healthcare environment are not that useful.

**Are you going to rank outcomes by country?**

No. We will be sensitive in how we report data.

Will my name be on the publication? What about my research nurse or trainee doctor?

Yes, that is our intention. The study steering committee (SSC) want to have an inclusive authorship policy and this is set out in the protocol. If you've contributed towards the conduct of Squeeze as a national co-ordinator, principal investigator or co-investigator then we want to recognise your work and include you in the 'Squeeze investigators'. There is precedent with projects that have resulted in publications with hundreds or thousands of authors, like when EuSOS was published in the Lancet in 2012 (<https://www.ncbi.nlm.nih.gov/pubmed/22998715>) with almost 2000 authors. Or an analysis from ISOS published in Intensive Care Medicine (<https://www.ncbi.nlm.nih.gov/pubmed/28439646>) with over 2000 authors. However, similar publications in other journals, like the British Journal of Anaesthesia (<https://www.ncbi.nlm.nih.gov/pubmed/27799174>) or the European Journal of Anaesthesiology (<https://www.ncbi.nlm.nih.gov/pubmed/28633157>) list collaborators, rather than authors. Until the study analysis is complete we won't have decided the destination journal.

There is an authorship policy on the website that provides more details.

Why do I need ethical approval when I'm just collecting routine data?

Different countries have different approaches to studies that involve the collection of data from patients. Some may consider this to constitute research that requires individual patient consent, some would agree but have the capacity to waive individual patient consent, others may consider this to be an 'audit' and not require consent. The SSC consider that the ideal approach is waived informed consent because it minimises the risk of introducing selection bias. There is precedent – for example the ISOS study.

If consent is required, how to collect patient consent ?

Consent procedures and provision of patient information will be conducted in accordance with local practice.

prior to surgery, the patients will be presented the IRB-approved consent form that has to be signed by the patient before inclusion. When there is no time to collect consent prior to surgery or a patient is unable to give consent, according to the Principal Investigator's judgement, consent may be obtained after surgery. In this case consent must be obtained within 7 days of surgery, or as deemed



appropriate by Principal Investigator. Patients included in Cohort B can give their consent after surgery; this is because patients included in Cohort B will first be eligible for the study until it is known that they receive vasopressors postoperatively.

Why isn't my country's data going to be included in the main manuscript? This is unacceptable discrimination against low and middle-income countries.

As this study is funded and supported by a European organisation the priority is to consider healthcare environments that are most similar Europe (acknowledging that within Europe there is a degree of variation). Patient data from patients in all countries within the Council of Europe (47 member states), Canada and USA, Australia and New Zealand will be analysed and reported in the main manuscript.

Information from other continents (Africa, Asia and South America) is no less valuable but will be reported separately to avoid considering incomparable healthcare environments together.

Are the study documents available in my language?

Possibly, the list of national co-ordinators (NC) is available on the website. Some NCs may have created translations.

If the patient is discharged or dies before day 30, is their data still included in the study?

Once the initial data is acquired the patients stay in the study whatever the outcome. To ease the burden of data collection we do not expect patient's to be followed up after 30 days or after they leave hospital – if they're still alive at day 30 but die at day 32, they are counted as a survivor – because we're censoring at day 30. Similarly, if they are discharged from hospital at day 5 but die at day 17, they count as a survivor – because they're not expecting post-hospital follow-up.

How long is the study going on really?

We plan to collect data in spring 2020. Each country can decide one- or two-weeks during spring where data for cohort A is being collected in a one-week observation window. After that each hospital collect 30 consecutive patients that receive PVI. This may take several months. Some hospital that rarely give postoperative vasopressors may not reach that number by the end of the year 2020. Then we stop inclusion of patients and start analysing data.



What counts as surgery? What about endoscopy or radiology?

It is very difficult to give a definitive answer to this question and there will always be a degree of subjectivity to this. There are extremes where it is clear – for example an open surgical procedure conducted by a trained surgeon in an operating room under general anaesthesia is clearly surgery. Whereas a diagnostic upper gastrointestinal endoscopy performed by a medical gastroenterologist in an endoscopy suite under conscious sedation is clearly not surgery.

Procedures that are diagnostic are not surgery. Procedures that include an element of intervention, may be considered surgery in some situations. Please remember that any procedure that is day case is not included.

The ‘grey area’ includes where an intervention is performed, but it’s not by a surgeon, no anaesthesia is given, or it’s not done in an operating theatre.

Example 1: I would not consider a percutaneous tracheostomy performed by an intensivist on the intensive care unit as an operation but in some hospitals, this same procedure might be undertaken by a surgeon in an operating theatre and it might be considered as surgery under these circumstances.

Example 2: I would not consider a percutaneous endoscopic gastrostomy performed by a medical endoscopist (or a radiological implanted gastrostomy performed by a radiologist) to be surgery. A very similar procedure performed in an operating theatre by a surgeon might be considered surgery. Again, if the patient is planned to go home the same day then it shouldn’t be included.

Ultimately it will be up to the local PI to decide and if they are uncertain, they can ask their NC. **If in doubt – it’s not surgery.** We would like to exclude relatively trivial interventions.

What about patients who are on vasopressor infusions before surgery?

This is uncommon but does happen and we are interested in this. Therefore, there is a field in the eCRF to record this. If the patient fulfil the standard criteria for PVI then CRF2 needs to be completed – like every other patient.

Who do I contact to get additional Open Clinica login details?

We will create access for PI and secondary contact and if needed additional access (max 5 can be created). To obtain additional access accounts please contact: squeeze@esaic.org



Clinical Trial Network



Please note – there is a separate FAQ for the eCRF