* **Scientific Title** A randomized comparison of the effects of Propofol versus Sevoflurane on cerebral autoregulation when conducting general anaesthesia for robot-assisted prostate surgery.
* **Simplified Title** Effects of Propofol versus Sevoflurane on control of brain blood flow during robotic surgery.
* **Investigators** Mr Tomas Robertson, Dr Tim McCulloch, Dr Michael Paleologos, Dr Ruban Thanigasalam and Dr Scott Leslie
* **Aim** To investigate differences in cerebrovascular physiology between classes of anaesthetic agents in patients undergoing robotic abdominal and pelvic surgery
* **Hypothesis** Ho: There will be no difference in cerebral autoregulation between the patients undergoing Propofol anesthesia versus volatile anesthetic agents.

Ha: Cerebral autoregulation will be less likely to be impaired with Propofol-based aneasthesia compared with Sevoflurane-based anaesthesia.

* **Background** Currently there is no standard anesthetic agent recommended for robotic pelvic and abdominal surgery (Herling *et al.* 2016).Anaesthetic agents have variable effects on the cerebral vasculature and as such it has been hypothesized that one may be more suitable for robotic pelvic and abdominal surgery than the others. For instance, Sevoflurane, a volatile anesthetic agent, increases cerebral vasodilation and hence decreases vascular resistance (Conti *et al.* 2006). This may impair cerebral autoregulation (Conti *et al.* 2006). Conversely, Propofol was not found to significantly modify cerebral haemodynamics (Conti *et al.* 2006). It has been reported that cerebrovascular markers have remained within safety limits under Sevoflurane maintained anaesthesia during surgery in the steep Trendelenburg position (Kalmar *et al.* 2010). A feature of robotic surgery is the requirement for carbon dioxide pneumoperitoneum in conjunction with steep head-down positioning. We hypothesise that the cerebrovasodilatory effects of carbon dioxide combined with the potential for oedema from head-down positioning could render the brain particularly susceptible to the vasodilatory effects of volatile anaesthetics, including sevoflurane.
* **Research Plan**

 Study Type Randomised controlled trial

##  Setting/Location Theatres at Royal Prince Alfred Hospital (RPAH) and Chris O’Brien Lifehouse.

 Duration of Study 12 months

 Methods

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| Study Population | Ages 18 years and over with both males and females accepted. |
| Recruitment | Patients will be invited to participate upon consultation with their surgeon prior to their surgery. Participants at RPAH will be given the Patient Information Sheet and Consent Form prior to surgery in the RPAH Pre-Admission Clinic, with final consent obtained on the day of surgery.Participants at Chris O’Brien Lifehouse will receive the Patient Information Sheet and Consent Form in the surgeons’ private consulting rooms (Dr Ruban Thanigasalam and Dr Scott Leslie) prior to surgery, with final consent obtained on the day of surgery. |
| Number of patients | 30 |
| Key Inclusion Criteria | Robotic prostate surgery in the steep Trendelenburg position |
| Key Exclusion Criteria | History of cerebral vascular diseaseIntracranial pathologyAllergy to Propofol.Contraindication to Sevoflurane, including malignant hyperthermia or history of severe postoperative nausea and vomiting. |
| Study Treatment/Intervention | 1. Randomisation to either sevoflurane or propofol as the prime anaesthetic agent.
2. Intraoperative cerebral autoregulation testing.
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| Randomisation and blinding | Online software will be used to create randomised permuted blocks. We will create 3 blocks of 4 and 3 blocks of 6 (total 30 subjects) and will randomise the order of the blocks.Opaque envelopes marked with the study number will contain a piece of paper with the name of the allocated anaesthetic agent.The patient will be blind to group allocation.The treating anaesthetist and investigator will be aware of the anaesthetic agent during data collection.Investigators will be blind to the agent at the time of data analysis. |
| Outcome Measurement | The primary outcome measure in this study will be the Cerebral Autoregulation Index (ARI) assessed using a Transcranial Doppler. .  |
| Statistical Considerations/Data analysis | Minimum meaningful difference to detect $δ$: 0.3 (Schramm et al. 2014)Significance level ($α)$:$α=$0.05, z$α $= 1.96Power (1-$β$): Set power at 80%, z2$β$=0.842Standard deviation: $σ$=0.25 (Schramm et al. 2014)n$\geq $2(z$α$+z2$ β$)2($\frac{σ}{δ}$)2n$\geq $ 2(1.96+0.842)2($\frac{0.25}{0.3})$2n$\geq $ 10.90Therefore a minimum of 11 people will be needed in each arm of the trial in order to have an 80% probability of finding a difference in ARI of 0.3 with a standard deviation of 0.25 As we are comparing two independent means, a student’s two sample t-test will be used to determine if there is a significant difference between the ARI of those under Propofol anaesthesia compared with Sevoflurane.  |

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| --- | --- |
| Ethical Considerations | The main ethical consideration with perioperative anaesthetic research is contacting the patient early enough to give adequate time for the patient to consider their decision to participate. Patients will be invited to participate upon consultation with their surgeon prior to their surgery. Participants at RPAH will be given the Patient information sheet and consent form prior to surgery in the pre-admission clinic. Participants at Chris O’Brien Lifehouse will receive the Patient Information Sheet and Consent form in the surgeons’ private consulting rooms prior to surgery (Dr Ruban Thanigasalam and Dr Scott Leslie), with final consent obtained on the day of surgery. |
| Safety Considerations | There are no known safety considerations regarding the choice of anaesthetic agent. Both agents in this study are routinely used and there is no proof that one is superior to the other. Either Propofol or sevoflurane (or even a combination of the two) are given to most patients currently having this procedure.Autoregulation testing involves deliberate manipulation of the blood pressure. We will use a phenylephrine infusion to control the blood pressure. Phenylephrine is a standard drug used during anaesthesia to support blood pressure. Many patients would receive this drug, regardless of their participation in this study. The range of blood pressures used to test autoregulation (mean arterial pressure 80 mmHg to 100 mmHg) is within the normal range of blood pressure considered acceptable during general anaesthesia in patients undergoing major surgery.Changes in cerebral blood flow will be detected with transcranial Doppler (TCD). This is an ultrasound technique of minimal or negligible risk. There is a theoretical possibility of tissue damage from pressure from the ultrasound probe but we have not seen this after over decades of using TCD routinely in patients having carotid surgery. |
| Investigator obligations | Storage of data will take place on REDCap. Any adverse outcomes potentially related to the study will immediately be notified to the SLHD HREC. Adverse events will be monitored using standard observational equipment. Adverse events will be recorded on REDCap. |
| Funding | The major sponsor of this study is the Sydney Local Health District (SLHD). No additional equipment or medications are required other than those already available within the institutional resources. |
| Conflict of Interest | No conflicts of interests |

* **Outcomes and Significance**

Cerebral oedema is a recognised, although rare, complication of robotic prostate surgery. These are long procedures with the patient in a steep head-down position. Previous studies have investigated some of the cerebral haemodynamic effects of general anaesthetics during this type of surgery, but we are unaware of any studies comparing different anaesthetic regimens with respect to their effects on cerebral autoregulation.

There is significant potential for adverse post-surgical outcomes following robotic prostate surgery (Kalmar *et al.* 2010). It has been suggested by several studies that further research is needed into the different outcomes of anaesthetics used in robotic pelvic and abdominal surgery in order to minimise complications (Kalmar *et al.* 2010, Herling *et al.* 2017). This study will add to the knowledge of the cerebrovascular effects of general anaesthetics during robotic pelvic and abdominal surgery, for which there is no currently recommended first line anaesthetic (Herling et al. 2017).

**Study Design:**

Inclusion criteria:

* Age 18 years or older
* Scheduled for robot-assisted prostatectomy at RPAH and Chris O’Brien Lifehouse
* Capable of giving informed consent

Exclusion criteria:

* Contraindication to sevoflurane, e.g. susceptibility to malignant hyperthermia, history of severe postoperative nausea and vomiting.
* Contraindication to Propofol, e.g. history of allergy to Propofol
* Intracranial pathology
* Cerebrovascular disease
* Morbid obesity (BMI >35)

Conduct of general anaesthesia

* Monitoring of vital functions will be according to standard practice at RPAH and Chris O’Brien Lifehouse for robotic surgery and will include invasive arterial pressure monitoring via a radial artery catheter, respiratory gas monitoring including carbon dioxide, inspired oxygen, and end-tidal agent monitoring (in the Sevoflurane group).
* The effect of the general anaesthetic agent on the frontal encephalogram will be monitored with a BIS® monitor. To ensure comparable doses of the anaesthetic agents, at the time of autoregulation testing the dose of general anaesthetic agent will be adjusted to target a BIS score of 45 ± 5.
* Propofol group: propofol, which is an intravenous anaesthetic agent, will be administered by a commercial microprocessor-controlled pump running a target-controlled infusion algorithm. This is routine practice at RPAH and Chris O’Brien Lifehouse.
* Sevoflurane group: Induction of anaesthesia will be with a bolus of propofol, after which anaesthesia will be maintained via inhalation of sevoflurane. There will be no residual effects of the induction-dose of propofol by the time autoregulation testing commences. Whilst induction by inhalation of sevoflurane would be possible, inhalational inductions is sometimes poorly tolerated and it is more common at RPAH and Chris O’Brien Lifehouse for patients receiving sevoflurane to be induced with a small dose of propofol.
* Both groups:
	+ The intraoperative opioid will be remifentanil, administered by a target-controlled infusion with a targeted effect-site concentration of 2 mcg/mL - 4 mcg/mL. After completion of the study, the treating anaesthetist may choose to change the intraoperative opioid, and/or add other analgesic therapies (e.g. ketamine).
	+ The general anaesthetic will consist of either sevoflurane or propofol combined with remifentanil. This will preclude co-administration of nitrous oxide, ketamine, and any other general anaesthetic agent. After completion of autoregulation testing, the study is completed and these or other anaesthetic drugs can be administered at the discretion of the treating anaesthetist.
	+ At the time of autoregulation testing, inspired oxygen will be standardised at 30 mmHg – 35 mmHg, unless a higher concentration is required to maintain arterial oxygen saturation ≥ 94%.
	+ At the time of autoregulation testing, ventilation will adjusted to achieve arterial partial pressure of carbon dioxide of 40 ± 2 mmHg, confirmed on arterial blood gas analysis.
	+ A phenylephrine infusion will be administered if vasopressor support is required for blood pressure control prior to autoregulation testing.
	+ Transcranial Doppler (TCD) monitoring will be established after positioning of the patient and after commencement of the surgery. TCD monitoring involves:
		- A padded plastic frame is snuggly placed around the patient’s head.
		- The TCD probe is attached to the frame and positioned against the skin overlying the temporal bone on one side of the head and adjusted to acquire a Doppler signal from the middle cerebral artery.
		- The ultrasound power is reduced to the minimum required to maintain a reliable signal.
* Autoregulation testing:
	+ Autoregulation testing will be performed at times when there is minimal or constant surgical stimulation and the patient is judged to be haemodynamically stable.
	+ Autoregulation testing will be performed:
		- Immediately prior to moving the patient to the steep head down position.
		- Hourly while in the steep head-down position.
	+ If mean arterial pressure (MAP) is >80 mmHg, the phenylephrine infusion will be reduced and/or the remifentanil infusion increased until MAP is ≤80 mmHg.
	+ While recording middle cerebral artery blood velocity, the phenylephrine infusion will be gradually increased until MAP is ≥100 mmHg.
* Data management
	+ Data analysis
		- The TCD waveform and the arterial pressure waveform will be digitally recorded to a laptop computer.
		- In subsequent data analysis, the autoregulation index (ARI) is calculated using a standard formula and patients will be classified as having either normal autoregulation, ARI >0.4, or impaired autoregulation, ARI≤0.4. (Constant cerebral blood flow despite the change in MAP gives an ARI = 1.0, whereas cerebral blood flow changing completely passively with MAP gives an ARI = 0.0)
	+ Data storage and security
		- Data will be stored on a REDCap Database saved on the secure SLHD server.
	+ Access, sharing, reuse of data
		- All paper records will be stored in a central location with restricted access in locked file cabinets within the Anaesthetics Department, RPAH. Access will only be granted to designated research staff. The data will be stored on the password protected PC located in the Anaesthetics Department. The access to this room is restricted to the personnel included in the protocol and the data will be stored on the secure SLHD server.
	+ Data retention and disposal
		- All data and written records related to the study will be kept for a minimum of 15 years before being destroyed.
* Adverse events
	+ Adverse events will be monitored using standard surgical observation equipment including: Blood pressure monitoring, arterial oxygen saturation, arterial carbon dioxide partial pressure and ventilation rate.
	+ Adverse events will be recorded in REDCap after both attending anaesthetist and surgeon are informed.
	+ Serious Adverse Events (SAE)
		- All Single case Adverse Events (AEs), Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs), significant safety issues (SSIs), any local SUSARs/ Unanticipated Serious Adverse Device Effects (USADEs)/ Unexpected and Related Serious Adverse Event (URSAEs) arising from the site and any research-related events that meet the definition of an incident will be submitted by the investigator to the local RGO.
* Dissemination strategy
	+ Study participants:
		- Study participants will receive a lay summary of the results of the study
	+ Healthcare professionals
		- The results of the research will be published in the relevant journal.
	+ Limitations on publication will be determined once the appropriate journal is selected

Demographic and other data. The following data will be collected for each patient:

* Age
* Gender (all patients will be male)
* Weight
* Height
* Routine preop medications
* Co-morbidities:
	+ Cardiovascular: hypertension, known ischaemic heart disease
	+ Respiratory: asthma, chronic obstructive airways disease
	+ Diabetes
* Time of induction of anaesthesia
* At the time of each autoregulation test:
	+ BIS score, End-Tidal CO2, PaCO2
	+ Dose of remifentanil (effect site target concentration)
	+ Dose of propofol (effect site target) or sevoflurane (end-tidal and age-adjusted MAC))
	+ Volume of intravenous crystalloids infused
* Any anaesthesia-related complications

* **References**

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