Cleveland Clinic Florida

Correlation between vasopressin and renal function following a controlled intraabdominal pressure elevation

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INVESTIGATOR'S SIGNATURE PAGE

Protocol number or version: _____V.4_____

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal regulatory requirements and applicable US federal regulations and ICH guidelines.

Investigator:

Signed: _____ Date: _____

Name and Title

(PAGE TO BE PRINTED AND SIGNED WITH EACH FINAL PROTOCOL VERSION)

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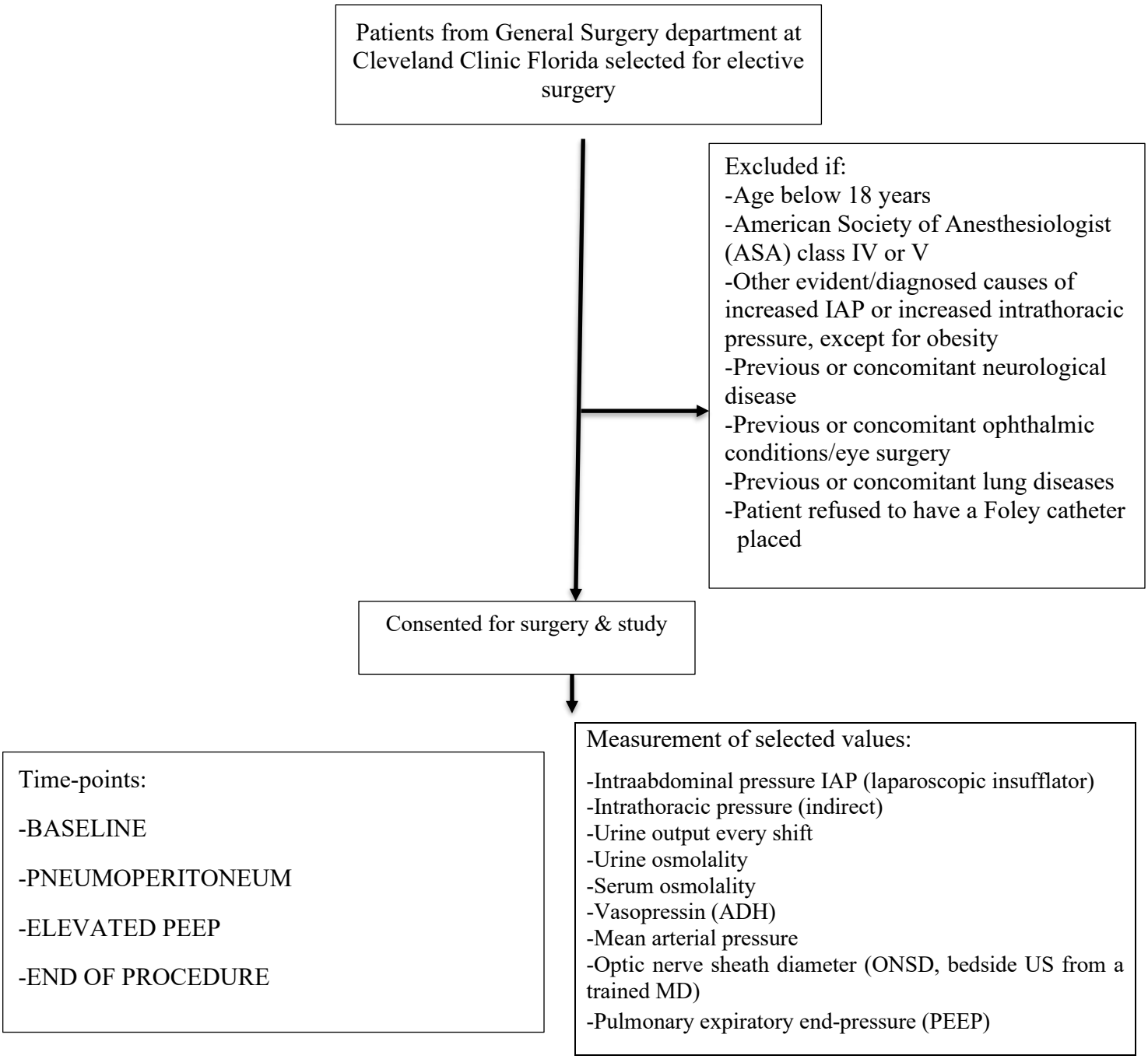
REASEARH SCHEME



1. INTRODUCTION

1.1 Context:

Increase in intraabdominal pressure (IAP) has been demonstrated to correlate with consequential hemodynamic effects. Several studies have been carried out mostly in experimental settings to define the underlying mechanisms that regulate the pathophysiology following an increase in IAP. In the last years this topic has become concerning because of the wide spread of laparoscopy, that is namely an iatrogenic acute increase in IAP.

Despite most consequences affecting cardiovascular, renal and pulmonary systems could be fairly explained by mechanical/compression insults following increased IAP, there is still lack of knowledge about the neurohormonal responses involved. Many authors have demonstrated the correlation between abdominal and intracranial pressure, which might explain the basis for neurohormonal regulations. There are two mechanisms postulated that could explain these phenomena. An early mechanical stage is explained by compression of the inferior vena cava from a cranial displacement of the diaphragm caused by the insufflation of pneumoperitoneum, which reduces the venous drainage from the lumbar plexus and central nervous system, thereby increasing the pressure in the cerebrospinal fluid[1]. A late arterial mechanism is related to CO2 diffusion through the peritoneal membrane, which results in an increase in PaCO2 and a reflex vasodilation that leads to an increase in intracranial pressure (ICP), following the Monroe-Kellie hypothesis[2,3].

The effects of an elevated ICP on renal hemodynamics have been studied under experimental and clinical setting, though not fully understood[4,5]. Decreased cardiac output and increased vascular and renal resistance were proposed as mechanisms underlying the sudden impairment in renal function following an increased intraabdominal pressure, although correcting the cardiac output did not restore a

normal renal function. Also, placing ureteral stents to counteract high pressure compression on ureters, did not restore a normal urine output either[6].

Catecholamines and vasopressin release has been proposed to have an important role in this mechanism[7-10]. About this topic studies have been carried out with the aim of identifying significant antidiuretic hormone changes during laparoscopy and position changes[9,10].

Furthermore, several studies have validated the use of optic nerve ultra sound as a non-invasive, accurate, safe, reproducible and cost-effective tool in assessing intracranial pressure (ICP), reducing potentially harming consequences of invasive transcranial measurements[11-13].

2. OBJECTIVES

In a standard operative setting as for sleeve gastrectomy, endotracheal ventilation is routinely administered to patients under general anesthesia. Positive expiratory end-pressure (PEEP) effect on increasing IAP is controversial, still its effect on increasing intracranial pressure (ICP) is widely accepted[14].

The aim of this study is to investigate any direct correlation between increased intrathoracic pressure, intraabdominal pressure and intracranial pressure, following a controlled elevation in intraabdominal pressure and intrathoracic pressure (PEEP). The second end-point is to investigate any correlation between elevated intracranial pressure and vasopressin release, urine output and urine and serum osmolality by measuring their values at different time-points.

3. STUDY DISIGN

3.1 General design:

This study is a prospective study involving patients selected for elective surgery. Patients undergoing bariatric surgery will be enrolled in this study and have several parameters checked as explained below.

3.2 Setting/Participants:

The study will take place in Cleveland Clinic, Florida in a standard operative setting. An estimated number of patients, based on statistical power analysis, undergoing a Sleeve Gastrectomy will be enrolled to participate in this study.

3.3 Study Interventions and Measures:

Patients selected and consented for elective surgery will undergo standard of care and additional measurements during and after surgery. These measurements involve minimal risk as the probability and magnitude of physical or psychological harm anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or in routine medical, dental, or psychological examinations. In order to support our pathophysiological hypothesis, we identified 4 different conditions in which the measurements should be done:

A) Baseline
B) Patient under general anesthesia, 10-15 minutes after insufflation of pneumoperitoneum at 15mmHg, PEEP at 5cmH2O or lowest setting
C) 10-15 minutes after stabilization of PEEP at 10cmH2O, pneumoperitoneum still at 15 mmHg
D) 10-15 minutes after desufflation of pneumoperitoneum and basal mechanical ventilation

Measurements include:

-Intraabdominal pressure IAP: assessed via laparoscopic insufflator, set at 15 mmHg as a standard value for all laparoscopic procedures

-Intrathoracic pressure: indirectly measured by variability of peak expiratory pressures

-Urine collection: Urine output will be measured every shift by the nursing staff from the beginning of surgery to post-operative day 1.The use of Foley catheters during these laparoscopic procedures is dependent on the surgeon's judgment based on patient's co-morbidities. However, in order to participate in this study a Foley catheter needs to be inserted, so the patient will receive a Foley catheter. It will be removed Post-operative day 1.

-Urine osmolality prior to surgery and 8-12 hours post-surgery

-Serum/plasma collection: blood draws to evaluate specific values of

-Plasma Vasopressin (ADH)

-Serum osmolality

-Mean arterial pressure: noninvasive standard anesthesia monitoring

-Pulmonary expiratory end-pressure (PEEP): anesthesiologists routinely adapt PEEP in order to maintain an optimal ventilation, especially in obese patients and during laparoscopy

-Optic nerve sheath diameter (ONSD): B scan with a 7.5-MHz linear ultrasound probe to measure the diameter of the optic nerve sheath 3 mm behind the globe is going to be used. Dr. Lisandro Montorfano, a trained ultrasonographer, under the supervision of an anesthesiologist will take the non-invasive sonographic picture by gliding the probe over the eyelid while the participants are under anesthesia.. The ONSD will be measured from the captured picture. Study personnel will record the interaction on the patient's chart and include the measurement in the database.

3.4 Primary study endpoint

- Find a direct and significant correlation between increased IAP level (iatrogenic induced and controlled), ICP, ONSD, vasopressin release and urine output
- Two different pathophysiological mechanisms could potentially elicit an increase in ICP (pneumoperitoneum and PEEP), so that the most accounting mechanism may be investigated and in what proportion

Expected results:

- At higher IAPs (time-points B and C), an increase in vasopressin serum levels, a decrease in urine output and renal function with increased urine osmolality are expected. A significant increase in ONSD is also expected.
- At IAP normalization (time-points A and D), a decrease in vasopressin serum levels and restoration of renal function and urine osmolality are expected.

Limitations:

- Obesity is a well-known chronic condition of increased intraabdominal pressure, but a baseline measure is provided and acute variations will be investigated, therefore minimizing this potential bias
- All the measurements except for urine collection are assessed during surgery and perioperatively, so eventual late variation may be missed, despite sought homeostasis responses are thought to operate in rapid circumstances

3.5 Primary safety endpoints

- The study should be stopped if the patients experience any symptoms or complications due to the interventions implemented.
- The need of opioid will be assessed by the pain score scale and will be restricted to the minimum level required to control the patient's pain and to

provide optimal comfort, as opioid administration may be a confounding element in vasopressin release[15]

- All the measurements will pose minimal risk to the patient. ONSD assessment is non-invasive and safe. Urine collection is routinely assessed during Sleeve Gastrectomy by meaning of a Foley catheter. Blood draws pose only minimal risk to the patient. Urine output is measured every shift per the nursing staff as standard of care.
- Variations in PEEP level are currently performed during general anesthesia, especially in obese patients and during laparoscopy; according to this study design are supposed to be transient and controlled, therefore not potentially dangerous to patient's intra- and post-operative ventilation

4. SUBJECT SELECTION AND WITHDRAWL

4.1 Inclusion criteria

- Patients scheduled for Sleeve Gastrectomy will be eligible

4.2 Exclusion criteria

- Age below 18 years
- American Society of Anesthesiologist (ASA) class IV or V
- Other evident/diagnosed causes of increased IAP or increased intrathoracic pressure, except for obesity
- Previous or concomitant neurological disease
- Previous or concomitant ophthalmic conditions/eye surgery
- Previous or concomitant lung diseases
- Patient refused to have a Foley catheter placed

4.3 Subject recruitment and screening.

Patients scheduled for elective Sleeve Gastrectomy, according to bariatric surgery eligibility criteria, will be recruited from the General Surgery outpatient department at Cleveland Clinic Florida.

4.4 Early withdrawal of subjects

Patients may withdraw from the trial at any time and for any reason. Some possible reasons of withdrawal include the following:

- Development of any medical condition or need for concomitant treatment that precludes further participation in the trial.
- Unacceptable adverse event due to the suggested study interventions.
- The investigator removes the patient from the trial in the best interest of the patient.
- Patient withdraws consent to continued participation in the trial.

5. STATISTICAL PLAN

This is the sample size calculation for identifying significant increase in vasopressin release after an elevation in intra-abdominal pressure.

Study Design:

Patients undergoing a Sleeve Gastrectomy are to be enrolled to participate in the study. 4 different conditions in which the measurements should be done during and after the surgery:

A) Baseline

B) 10-15 minutes after insufflation
C) 10-15 minutes after stabilization
D) 10-15 minutes after desufflation

Primary aim:

Expecting 20-25% increase in the normal value of vasopressin significant for the study purpose.

Assumptions:

- The normal range value of vasopressin is from 1 to 4pg/ml. According to the number stated in the reference articles, we assume the coefficient of variation is 0.455.
- The type I error rate for the overall test comparing the three groups will be 0.05.
- There would be six pairwise group comparisons: A vs B, A vs C, A vs D, B vs C, B vs D, C vs D; the type I error rate for each comparison will be 0.0083(Bonferroni correction) and the data were assumed to be log-normal distributed.
- Power was computed based on 80%.

Statistical Method:

Repeated measures ANOVA is used to compare the means sore of vasopressin across four different conditions. The comparison between any two conditions is accessed using paired t-test. To adjust for the multiple test problem, Bonferroni correction is applied and the type I error rate for each comparison will be 0.0083.

Result:

Plausible sample size for any two conditions comparison with 25% vasopressin increase should be 57

Table 1. Sample Size Calculation			
Increase Rate	**Nominal Power**	**Actual Power**	**N**
20%	0.8	0.802	83
20%	0.9	0.900	104
25%	0.8	0.806	57
25%	0.9	0.902	71
30%	0.8	0.803	42
30%	0.9	0.907	53

6. SAFETY AND ADVERSE EVENTS

6.1 Recording of adverse events.

The clinical course of each adverse event will be followed until resolution, stabilization or until it has been determined that the study interventions or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

6.2 Reporting of serious adverse events

6.2.1 IRB notification by investigator

1. Adverse events which are serious, unexpected and related or possibly related to participation in the research.

2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity that expected.

3. Other unexpected adverse events, regardless of severity, that may alter IRB analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the researcher protocol or informed consent process/document.

4. Unanticipated problems involving risks to subjects or other or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.

6.3 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, the circumstances and procedures for interrupting or stopping the study will be clarified. The stopping rules should be incorporated into the data safety analysis plan as well.

6.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 8 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7. DATA HANDLING AND RECORD KEEPING.

7.1 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

7.2 Source Documents

Source data will include the electronic health record for patient demographics, vitals, and basic laboratory results. Dictated operative notes will be maintained within the EHR as well. Lab results of inflammatory markers will be kept out of the EHR and kept in a secure file on the Cleveland Clinic server.

7.3 Records Retention

The investigators will retain study essential documents for at least six years after completion of the research and are accessible for inspection by authorized representatives at reasonable times and in a reasonable manner.

8. STUDY MONITORING, AUDITING AND INSPECTING

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and Institutional compliance and quality assurance groups of all study related documents (for example, source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (for example, pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices

9.0 ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor [if applicable] before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision

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11. APPENDIX

Optice Nerve Ultrasound

In the operating room, patients are placed in a supine position and intubated, with both eyes protected by patches. Using an ultrasound with a 12-MHz transducer (General Electric Venue 40, USA), the diameter of the ONS is measured at a standard level of 3 mm from its origin in a single eye. The ultrasound machine is kept in the anesthesia work room and available upon request to the anesthesia technician. Before and after each use the probe is cleaned with alcohol pads. A specific ultrasound probe cover is utilized during contact with the patient's eye lid.