American University of Armenia

Department of Public Health

GASTROPROTECTIVE MEDICATIONS IN PRIMARY AND SECONDARY PREVENTION OF STRESS ULCERATION IN ADULT PATIENTS UNDERGOING CHOLECYSTECTOMY

Randomized Clinical Trial

(Research Grant Proposal)

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Abstract

Magnitude of the problem: According to the literature, stress ulceration was detected in 50%-60% of patients who underwent appendectomy, phlebotomy, and cholecystectomy. There is evidence that the incidence of bleeding from the stress ulceration after cholecystectomy is more than 13 %. When bleeding from stress ulcer occurs, the mortality rates could reach 40%-70%, and in case of significant hemorrhage even exceed 80%.

Study Objective: to determine whether a gastroprotective medication, particularly proton-pump inhibitor pantoprazole, administered within the perioperative period decreases the rate of stress ulceration and the rate of stress ulcer complications (bleeding) in adult patients undergoing cholecystectomy.

Methodology: A prospective randomized clinical trial. Participants (target population): hospitalized patients undergoing open cholecystectomy. Setting: Clinical Hospital # 3, "Armenia" Medical Center. Inclusion criteria: patients aged from 18 to 65 years will be eligible for the study. Exclusion criteria: a) preliminary history of peptic ulcer disease; b) endoscopically proved gastric or duodenal erosions and/or ulcers; c) admission for emergency surgery; d) contraindications to the proposed therapy; e) mental health problems; f) pregnancy; g) breast-feeding; h) refusal to participate for any reason. Participants will be divided into *2 groups* - experimental (patients who receive pantoprazole (protonix) within pre- and early post-operative periods) and control (patients who receive placebo). *Randomization* will be carried out after *informed consent* has been obtained.

Sample size: The required sample size estimated by Stata (power method of calculation) is equal to ***300 patients***.

Data analysis will be done with the use of logistic regression model to estimate a summary odds ratio after adjustment for confounders.

Time Frame: Total expected duration of the study is ***12 months***.

Budget: The overall estimated budget is about **$70,092.00**, which includes ***$60,690.00*** fixed expenses and ***$9,402.00*** reimbursable expenses.

Background information:

Stress ulcers are defined as acute gastric and/or duodenal mucosal lesions appearing either as multiple small mucosal defects (erosions) or single ulcers in the aftermath of potentially stressful events, such as burns, multiple trauma, sepsis, or major surgery (23, 28, 29, 32, 34, 36). Surgical operation can be considered as the classical model of stress (8, 13, 15, 16, 33, 34). Surgical stress evokes complex neuroendocrine and tissue responses aiming at defense from injury and recovery of body integrity, enable adaptation to changing situations such as those associated with surgery (3, 5, 11, 15, 17, 22, 27, 30, 37, 39, 40, 46, 48, 52, 55, 58, 60). However, this response may become excessive and contribute to an increase in postoperative morbidity and mortality (2, 7).

Several studies found that the rate of stress ulceration after abdominal surgery ranges between 50% and 95% (28, 29, 32, 34). According to the literature, acute (stress) ulceration of the gastric and duodenal mucosa was identified in 11%-24% of patients who died at the surgical departments in general (14, 32, 34). Stress ulceration was detected in 50%-60% of patients who underwent appendectomy, phlebotomy, and cholecystectomy (28). The rate of bleeding from stress ulceration ranges from 5% to 60% and more (13, 28, 32, 34). There is evidence that the incidence of bleeding from the acute stress ulceration after cholecystectomy is greater than 13 % (66). When bleeding from stress ulcer occurs, the mortality rates could reach 40%-70%, and in case of significant hemorrhage even exceed 80% (28, 29, 32, 33). Nevertheless, it should be noted that when the investigators specifically studied this problem, they mentioned very high rates of stress ulceration and its complications (bleeding), otherwise, the researchers usually did not indicate any numbers. This can be explained by the fact that the only objective method to detect stress ulceration, or confirm this diagnosis and rule out other sources of bleeding, is

endoscopy (23, 28, 29, 32, 34). This procedure is rarely performed during the preoperative assessment of patients and within the postoperative period. Besides, the data provided by the investigators generally had not been obtained from randomized studies. Hence, the true rate of stress ulceration after major surgery, particularly cholecystectomy, is not yet known. It should be noted that there is no official data or published study on stress ulceration in surgical patients in Armenia.

Lesions arise mainly in the proximal stomach, rarely in the gastric antrum or the duodenum, usually within 72 hours after the stress insults (28, 29, 32-34, 36). Mucosal ischemia is the major pathophysiologic event responsible for acute stress ulceration (8, 28, 29, 32, 34, 36, 64). Although luminal acid is not the initial causal factor, when functionally weakened hypoxic mucosa is exposed to even physiologic levels of acids, erosions and/or ulcers may arise to cause life-threatening bleeding (17, 28, 29, 32, 34, 36). Like nonocclusive small bowel ischemia, ischemic colitis, and the "shock" liver syndrome, gastric "stress ulceration" is yet another component of the multiple organ failure syndrome (6, 45, 56). On the other hand, the level of organ dysfunction before surgery is one of the major risk factors for the development of stress ulceration and its complications (38). Other risk factors are aging (1, 53); family history of peptic ulcer disease (10, 47); blood group type 0 or A (10, 47, 63); mechanical ventilation equal or over 48 hours (24, 38); the duration of surgery (24); need for reoperation (53); use of non-steroidal anti-inflammatory drugs (NSAID) (1, 26, 47), corticosteroids (1, 10) or acetaminophen (10); *H. pylori* infection (47); heavy consumption of alcohol (1, 4, 47); smoking (1, 4, 10, 47); physical inactivity (12, 59); coffee consumption (63); low social class (63); type A personality (47) etc. Since all forms of therapy have yielded poor results, it seems reasonable to try to prevent ulcer development (28, 34, 43).

Pretreatment with antisecretory medications induces achlorhydria and results in reduction in the number of stress lesions (17, 36, 64). Inhibition of the gastric proton pump is gaining acceptance as the treatment of choice for the treatment of duodenal and gastric ulceration (50, 51). The gastric H^+/K^+-ATPase – the gastric acid pump – is the molecular target for the class of antisecretory drugs called the proton-pump inhibitors (PPIs) (51, 54). The research showed that along with antisecretory effect, PPIs increase gastric mucosal blood flow as measured by laser Doppler flowmetry (25). This can play an important role in gastric mucosal protection after stressful events. In contrast to other antisecretory medications, PPIs inhibit the terminal stage of acid secretion, and are, thus, more effective (21). Furthermore, due to the pharmacokinetic and pharmacodynamic characteristics of PPIs, they have less side-effects and interaction with other medications as compared with other gastroprotectors (9, 21). PPI-based triple therapy for *H. pylori* eradication appears to be the most cost-effective treatment option for *H. pylori*-related disease (9).

Pantoprazole, 2-[(2-pyridylmethyl)sulphinyl]benzimidazole, is a new substituted benzimidazole that inhibits the parietal cell H^+/K^+-ATPase (49). Pantoprazole is clinically superior to antacids and H_2-receptor antagonists in the treatment of acute duodenal ulcer, in term of both healing and symptom relief (21, 57).

Among PPIs pantoprazole has the lowest side effects and no proved interaction with other medications (41, 49, 62). Furthermore, pantoprazole is available as an intravenous formulation suitable for the administration to patients during the postsurgical period. In addition, no change in dosage is required when switching from oral to the intravenous pantoprazole (50, 65). No dose adjustment of pantoprazole is required for elderly patients or those with chronic renal or hepatic impairment, regardless of their severity (20, 49).

Intravenous pantoprazole has been shown to be effective and safe in clinical trials in the prevention of stress ulceration in Intensive Care Unit (21). However, no clinical trial has been conducted to evaluate the effect of pantoprazole in the prevention of stress ulceration in surgical patients. Potential hospital-based uses for intravenous PPI therapy include perioperative use as prophylaxis for acid aspiration syndrome during induction of anesthesia, prophylaxis for stress-related mucosal disease, and management of gastrointestinal bleeding from stress or acid peptic disease (50).

Based on above mentioned considerations, the following ***hypothesis*** is forwarded:

Gastroprotective medications, particularly, proton-pump inhibitors (pantoprazole), if administered during the perioperative period (preoperative period and early postoperative period), can decrease the rate of stress ulceration and its complications (bleeding) in patients undergoing major surgical operations, particularly cholecystectomy.

As a representative of major surgery, cholecystectomy has been selected for the following reasons. First, cholecystectomy is a one of the most frequently performed major surgical operations. According to the MOH of RA, approximately 15% of all abdominal operations conducted annually in Armenian surgical clinics represent cholecystectomy (42). Besides, it will be more feasible to advise patients admitted to the hospital to undergo endoscopy (esophagogastroduodenoscopy) for upper abdominal operations, like cholecystectomy, versus any other types of surgery. In addition, data suggest that the problem of stress ulceration is real for the patients undergoing cholecystectomy (28, 66).

Pantoprazole, as a representative of PPIs, is proposed to be used for the prevention of stress ulceration because of its superior effectiveness and safety in comparison to other

gastroprotective/antisecretory medications. Moreover, the availability of intravenous formulation makes pantoprazole as a medication of choice for the patients after surgical operations.

This project can provide a basis for other studies for the development of stress ulceration prophylaxis in surgical patients. The institution of effective prevention mechanisms, along with significant impact on medical sciences, will lead also to ***Public Health benefits***: better treatment outcomes and consequently increased quality of life of people, decreased loss of productivity, and decreased burden on the system.

Study Objective:

The objective of the study is to determine whether a gastroprotective medication, particularly proton-pump inhibitor pantoprazole, administered within the perioperative period, decreases the rate of stress ulceration and the rate of stress ulcer complications (bleeding) in adult patients undergoing cholecystectomy.

METHODOLOGY

A prospective randomized clinical trial (RCT) is the chosen design of the study. This selection has been made by the fact that RCT is the most reliable method ("gold standard") to test the efficacy of medication on treatment or prevention of particular diseases or pathological conditions. An important feature of such an experiment is that it is conducted on a sample of patients with a specific disease and as such, the data can be extrapolated to treatment of all patients with the same disease. The main appeal of the RCT in health/medical care derives from its potential to reduce of serious imbalance in unknown, but important factors, which could

influence the clinical course of the participants. No other design allows balancing these unknown factors.

Participants (target population): hospitalized patients undergoing open cholecystectomy.

Open instead of laparoscopic cholecystectomy is chosen since the rate of open cholecystectomy is much more higher in Armenia (42). Also, in contrast to laparoscopic surgery, open cholecystectomy is representative of major surgery with increased risk of development of postoperative stress ulceration. Furthermore, taking into consideration the cost of surgery and customary practice, people undergoing open cholecystectomy are commonly more representative to the general population than those with laparoscopic cholecystectomy.

Setting: Clinical Hospital # 3, "Armenia" Medical Center.

These hospitals were selected because patients treated there are representative to the whole population. Besides, taking into consideration that more than 400 cholecystectomies are conducted in these hospitals per year [personal communications], it provides an opportunity to complete the study within the time frame of 12 months. In addition, having two hospitals for patients' selection increase generalizability of study results.

Inclusion criteria: patients aged 18 to 65 years will be eligible for the study.

The rationale for the inclusion criteria is as follows:

The pharmacokinetics of pantoprazole have not been investigated in patients under the age 18. Besides, only patients of legal age can sign the informed consent form. With regards to patients over 65 years, it would be unethical to include them in the study because of the increased likelihood of side effects.

Exclusion criteria: a) preliminary history of peptic ulcer disease; b) endoscopically proved gastric or duodenal erosions and/or ulcers; c) admission for emergency surgery; d)

contraindications to the proposed therapy; e) mental health problems; f) pregnancy; g) breast-feeding; h) refusal to participate for any reason.

Patients with a preliminary history of peptic ulcer disease and endoscopically proved gastric or duodenal erosions and/or ulcers will be excluded from the study since it may be difficult to differentiate between peptic ulcer disease (as preexisting condition) and stress ulceration (as new condition/complication) which could lead to bias and negatively affect the study results. Patients admitted for emergency surgery will be excluded from the study because they would not have a time for complete preoperative assessment. The rest exclusion criteria have been stated considering ethical issues.

Participants will be divided into *2 groups* - experimental (patients who receive pantoprazole within pre- and early post-operative periods) and control (patients who receive placebo).

Randomization will be carried out by drawing an opaque sealed card containing a letter indicating to which group patients are assigned after *informed consent* has been obtained. Drawn letter will be attached to the patient's Case Histories. Randomization increases the likelihood that the groups will be similar in regard to characteristics, which may affect prognosis. It assumes unbiased distribution of potential confounders. However, the randomization is not a guarantee of comparability, because chance may play a role in the process. For this reason data for prognostic factors will be obtained at the time of subject entry into the study.

Preoperative assessment of patients:

At the beginning of the study, all participants will be examined to measure baseline variables. All patients (both experimental and control groups) will undergo

esophagogastroduodenoscopy (EGDS) to determine the presence or absence of peptic ulcer disease and/or gastric/duodenal erosions and take biopsy for *H. pylori* test.

EGDS will be done by endoscopists using fiber flexible endoscope (existing in both hospitals) under the local anesthesia (spray) of the oral cavity and throat with Xylocaine (Lidocaine oral spray 10%). In addition, to relieve anxiety and provide sedation, all patients will be administered by 1 tablet (5 mg) of diazepam (valium) (swallowed with a cup of water, ≈100 ml) 45 minutes before EGDS. Nurses will deliver diazepam.

H. pylori test will be carried out by taking a sample (a biopsy) of the stomach lining during EGDS. A biopsy will be taken and sent for testing to the laboratory of "Diagnostica" Center. A urease test of the biopsy will be done (a urease test relies on detection of the very active urease enzyme produced by *H. pylori*).

Information on gender; age; blood type; family history of peptic ulcer disease; use of NSAID, paracetamol (acetaminophen), corticosteroids; smoking status; alcohol consumption; coffee consumption; the level of physical activity; body mass index; social class (member of "PAROS")[1] will be included in the study protocol. Likewise, the data on the presence of diseases associated with peptic ulcer disease or increasing the risk of stress ulcer development – antral atrophic gastritis, rheumatoid arthritis, COPD, hepatic cirrhosis, chronic renal failure, pancreatitis (47, 34) will be recorded. Given that high physical workloads are associated with increased mortality (31), the data on perceived level of work-time physical activity will be documented as well (Attachment # 3).

[1] PAROS beneficiary system registers and ranks the vulnerability level of households in Armenia. PAROS database is now used by the Government of Armenia not only to determine the beneficiaries of humanitarian assistance, but also to target recipients under welfare programs.

Since the risk of developing of stress ulceration is increasing along with the number of detected organ dysfunction, the Multiple Organ Dysfunction Score will be calculated according to a modified version of Sauaia et al (44). Besides, the magnitude of stress associated with selected life events (within previous year) according to the Social Readjustment Rating Scale of Holms and Rahe (19) (revised) will be estimated because one of the most notable risk factors for the occurrence of upper gastrointestinal symptoms were found to be various indicators of psychological stress (particularly recent life events) (61) (Attachment # 3).

Intervention:

Pantoprazole (Protonix) produced by Wyeth-Ayerst Pharmaceuticals (USA) will be administered to the patients in the experimental group. US Food and Drug Administration (FDA) have approved this medication (67).

On the day before surgery, at 8 p.m. a nurse will give the patient 1 tablet (40 mg), delayed-release (enteric-coated), pantoprazole (protonix), which will be swallowed with a cup of water (≈100 ml). On the day of surgery (after the surgical operation) and on the 2 following days afterward, once daily, at 8 p.m. patients will receive an infusion of intravenous pantoprazole (protonix) through the intravenous cannula placed for anesthesia. Nurses will conduct this infusion according to the following instructions: dilute 40mg vial with 10 ml normal saline; use in-line filter provided by the manufacturer when infusing; maximum rate of infusion: 3 mg/min. Nurses will register in the study protocol all administrations of the medication.

Patients in the control group will receive placebo – an inert substance that looks, tastes, and smells like the active agent (pantoprazole). They will be provided by placebo in the regime and formulation similar to experimental group.

All medications (active and placebo) will be kept in special boxes with distinctive letters ("A" – for active medications; "B" – for placebo). Nurses will not be informed about the coding system. They will administer the medications according to the letter attached to the patients' Case Histories.

Assumptions

- All patients undergo the same general anesthesia. Thus, the type of anesthesia will not have an effect on the study results. Nevertheless, the type of anesthesia will be checked in the Study Protocol.
- Treatment of patients after surgery includes restoration of circulatory, respiratory and nutritional status, and adequate pain management; otherwise, it is unlikely that other methods will be successful in prevention of stress ulceration.
- It is assumed that, due to the randomization, patients with various personality types are equally distributed within 4 groups.

Postoperative assessment of patients:

EGDS will be performed on the 4^{h} day after the surgery for both patient groups to detect the presence or absence of stress ulceration or its complications (bleeding). EGDS will be done under the local anesthesia (spray) of the oral cavity and throat with Xylocaine (Lidocaine oral spray 10%). To relieve anxiety and provide sedation, all patients will be administered by 1 tablet (5 mg) of diazepam (valium) (swallowed with a cup of water, ≈100 ml) 45 minutes before EGDS. To minimize potential observer bias, endoscopists will be "blinded", i.e. they will not be informed about the group of patients they are examining.

The information on the duration of surgery and mechanical ventilation; reoperation; postoperative complications; and the level of surgeon's experience also will be included in the Study Protocol (Attachment # 3).

Principal outcome measures: the rate of stress ulcer development; the rate of stress ulcer complications (particularly, bleeding); stress ulcer mortality rate.

Other than the principal outcome measures: the rate of other than the stress ulcer postoperative complications; the rate of mortality from other than the stress ulcer causes.

Sample size:

The required sample size has been estimated by STATA computer program using power method of calculation. Before finalizing of assumptions for sample size calculation, several options have been checked (Table # 1).

Table # 1 Sample size calculation (power method) based on various assumptions

#	power	α	P_1*	P_2**	Sample size (for each group)	Sample size (total)
1	0.9	0.05	0.2	0.05	114	228
2	0.9	0.05	0.2	0.01	63	126
3	0.9	0.05	0.1	0.01	155	310
4	0.8	0.05	0.2	0.05	88	176
5	0.8	0.05	0.2	0.01	50	100
6	0.8	0.05	0.1	0.01	121	242

*P_1 - proportion of stress ulceration in control group
**P_2 - proportion of stress ulceration in experimental group

Among these options, the conservative one has been chosen:

power – 0.8; $\alpha = 0.05$; $p_1 = 0.1$; $p_2 = 0.01$; sample size (for each group) = 121;

sample size (total) = 242

To deal with possible dropouts, 58 more patients will be added to the required sample size. The total ***sample size*** will equal ***300 patients***.

The following is a Stata output of sample size calculation:

```
. sampsi 0.1 0.01, power(0.8)

Estimated sample size for two-sample comparison of proportions

Test Ho: p1 = p2, where p1 is the proportion in population 1
                    and p2 is the proportion in population 2
Assumptions:

         alpha =   0.0500  (two-sided)
         power =   0.8000
            p1 =   0.1000
            p2 =   0.0100
         n2/n1 =   1.00

Estimated required sample sizes:

            n1 =      121
            n2 =      121
```

Data collection and data entry

Data collection will last 10 months. Data will be recorded in the study protocol. Each protocol will be assigned a unique ID number consisting of three numbers/letters: the first one indicates hospital (number "1" – Clinical Hospital # 3; number "2" – "Armenia" Medical Center); the second one – sequential number of study participant (patient) in one particular

hospital; the third one – group to which each patient assigned (letter "A" – for the experimental group; letter "B" – for the control group). Data will be entered quarterly and completed by the end of data collection. To minimize possible data entry bias, double entry and data cleaning will be conducted. Data entry analysts will not be informed about the code of patients' assignment.

Data analysis

The statistical analysis of the data will be carried out using the STATA computer program. Statistical analysis will be done with the use of ***logistic regression model*** to estimate a summary odds ratio after adjustment for confounders.

The dependent variable is the rate of stress ulceration. The independent variables are gender; age; blood type; family history of peptic ulcer disease; *H. pylori* test; Multiple Organ Dysfunction Score; Social Readjustment Rating Scale; use of NSAID, paracetamol (acetaminophen), corticosteroids; the presence of diseases associated with peptic ulcer disease or increasing the risk of stress ulcer development; smoking status; alcohol consumption; coffee consumption; the level of physical activity; body mass index; social class (member of "PAROS"); duration of surgery and mechanical ventilation; # of reoperations and postoperative complications; the level of surgeon's experience.

The results will be presented with 95% confidence limit (α error tolerated – 0.05; power – 80%; two-sided test).

In addition, ***efficacy*** of the proposed intervention (gastroprotective medication – pantoprazole/protonix) will be calculated according to the formula: 1 – RR, where RR is a relative risk of the development of stress ulceration in the experimental group. Based on above mentioned assumptions (proportion of stress ulceration in the control group is equal to 0.1;

proportion of stress ulceration in the experimental group is equal to 0.01; thus, RR=0.01/0.1=0.1), the expected efficacy of the proposed intervention is equal to 90% (1-0.1=0.9). This is in accordance with the literature data showed almost 90% reduction in damage to the gastric mucosa by pantoprazole (21).

Quarterly preliminary data report will be presented to donor agency.

Potential biases and methods to handle them

Selection bias:

Selection bias occurs when the outcome of a clinical trial is affected by systematic differences in the way in which individuals are accepted or rejected for a trial, or in the way in which interventions are assigned to accepted individuals. Prevention of this bias is the main justification for the use of RCT to compare and evaluate different interventions in health care. However, random allocation of the participants to different study groups only increases the potential of a study to be free of bias. Therefore, RCTs are at risk of selection bias. Allocation concealment will help to prevent selection bias, protect the randomization sequence before and until the interventions are given to study participants. This means that the randomization sequence will be concealed from the investigators/project assistants at the time of obtaining consent from prospective trial participants. For this reason the randomization will be carried out by drawing an opaque sealed card containing a letter indicating to which group each patient assigned ("A" – for the experimental group; "B" – for the control group). These letters will be attached to the Case Histories of patients participating in the study. Project Manager will be the only person who knows the code. Thus, project assistants responsible for the randomization will

not know about the randomization sequence. In addition, project assistants will be trained on proper randomization practices.

Ascertainment bias:

Ascertainment bias occurs when the results or conclusions of a clinical trial are systematically distorted by knowledge as to which intervention each participant is receiving. Since the principal outcome measure of the proposed study is the rate of stress ulceration, which will be estimated based on the endoscopist's conclusion, the latter will be "blinded", i.e. they will not be informed about the group of patients they are examining.

Bias introduced by inappropriate handling of withdrawals, dropouts and missing information:

Ideally, all participants in a clinical trial should complete the study, follow the protocol, and provide data on all the outcomes of interest at all time-points. In reality however, most trials have missing data. Data can be missing because some of the participants drop out before the end of the trial, because participants do not follow the protocol either deliberately or accidentally, or because some outcomes are not measured correctly or cannot be measured at all at one or more time-points. Regardless of the cause, inappropriate handling of the missing information can lead to bias. To deal with the possible bias in these circumstances, the strategy of "intention to treat" analysis will be employed. This means that all the study participants will be included in the analyses as part of the groups to which they were randomized regardless of whether they completed the study or not.

Instrumental/measurement bias:

Instrumental bias may be created by the questionnaire contained in the study protocol. To minimize instrumental bias, the project assistants who will fill out the study protocol and the hospital personnel will be trained. Furthermore, questionnaire will be pre-tested.

The other possible source of bias could arise from the differences in performance and interpretation of laboratory analyses in two different hospitals, which could have an impact on assessment of patients' baseline variables. To deal with this problem, all necessary laboratory analysis will be carried out in "Diagnostica" Center, which is the authoritative/competent diagnostic institution in Armenia.

Study limitations:

- Since the second EGDS to detect the presence or absence of stress ulceration will be carried out on the fourth postoperative day, it is possible that stress ulcers developed after the fourth postoperative day would not be detected/diagnosed. Due to the fact that endoscopy is inconvenient procedure for the patients, it will be unethical/unfeasible to insist/advise them to undergo more than two endoscopies during the stay in the hospital. However, according to the literature, the overwhelming majority of stress ulcers develop within 72 hours after the surgery and, therefore, the number of undetected cases would be minimal.
- Taking into consideration that two different endoscopists at two separate hospitals will assess the presence or absence of ulceration, it is possible that there could be the variability of interpretation by the endoscopists. Nevertheless, it should be stressed that these two endoscopists have similar qualifications. Furthermore, there are personal observations that the diagnoses made by endoscopists are usually analogous [personal communications].

- Exclusion of patients over 65 years of age will affect the generalizability of study results to all adult patients' population. However, it will be unethical to include this contingent in the study taking into account the increased risk of development of complications.

ETHICAL ISSUES

Institutional Review Board or its equivalent will oversee the research. Participation in this study will be strictly voluntary. All participants will be provided by informed consent for their signature prior to entry in a study. Consent form will present a brief summary of the purpose and the nature of the clinical trial, likely risks and benefits, an explanation of the procedures to be followed and any drug to be used, a guarantee to guard the privacy of medical results, the voluntary nature of participation, the right to withdraw from the study at any time without prejudice to future medical care, right to question the investigator directly about the study. In addition, the participants will be provided with possible contacts of person in charge. The disclosure of information will be conducted in Armenian language (translation and accuracy will be approved by the Committee on Human Research).

Risk/Benefit:

The study poses more than minimal *risk* for participants since it includes intervention strategies on patients. Nevertheless, it should be noted that EGDS (with or without biopsy) is a procedure used at the discretion of the physician for the preoperative assessment of patients undergoing upper abdominal surgery. According to the literature, the risk of developing side effects due to endoscopy is very low (0.1-0.2 percent) and usually does not include life-threatening complications (18). Likewise, pantoprazole (protonix) is very well tolerated and was shown to be significantly superior on safety issues as compared to other PPIs or antacid

medications. The literature demonstrates that it has by far the lowest potential for interactions with other medications and side-effects, like diarrhea, headaches, nausea, abdominal/chest pain, rash, and pruritis, are observed only in rare cases (reported at incidences at 1% to 4% in various studies) (21). In addition, strict exclusion and inclusion criteria will contribute to minimizing of the risk for participants.

Participants will *benefit* from participation. The following benefits should be considered. If during the preoperative EGDS peptic ulcer disease and/or gastric/duodenal erosions had been detected, patients will be excluded from the study and will be provided a free of charge consultation regarding their illness and $50 for the course of treatment. If patients will develop stress ulceration or its complications (bleeding), they will be provided a free of charge consultation regarding their illness and $50 for the course of treatment prescribed by the qualified gastroenterologist/surgeon/ICU specialist. Also, the investigator will cover the cost of laboratory analyses. Finally, the potential health benefit of the study is a thorough examination of the patient, which could lead to more exact and comprehensive preparation of the patient for the surgery.

Confidentiality assurances:

The name and address or other identifying data of study subjects will be confidential. Giving a unique identifier to each subject will ensure confidentiality of participants. During data entry process the pages with identifiers will be separated. Only the study investigators will have access to the names and identification numbers of participants. Collected data will be stored at the American University of Armenia (AUA) for 3 years after completion of the study and then destroyed. The electronic datasets will be kept at the AUA.

Collaborative agreements:

Before the initiation of the study and in addition to the AUA IRB, the proposal will be sent to the Agency of Drug and Medical Technology of Armenia to get approval for the protocol and consent form. The letter of agreement will be obtained from the Directors of Clinical Hospital # 3 and "Armenia" Medical Center.

Institutional affiliation:

RCT will be conducted in affiliation with the Center of Health Services Research (CHSR) of the College of Health Sciences at AUA.

Dissemination of research results:

Research results will be disseminated through scientific publications, reports in scientific meetings, and implementation in practical medicine.

Time Frame for the Project:

Total expected duration of the study is 12 months (Appendix # 1).

Funding agency:

To get funding, the proposal will be presented to the interested donor agencies, particularly, Wyeth-Ayerst Pharmaceuticals (USA).

Budget:

The overall estimated budget for the proposed clinical trial is **$70,092.00**, which includes **$60,690.00** fixed expenses and **$9,402.00** reimbursable expenses (Appendix # 2).

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Appendix # 1

TIME FRAME FOR THE PROJECT

Activities*	**Months**											
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
1. Getting final approval from the IRB and Agency of Drugs and Medical Technologies of Armenia	*											
2. Hiring and training of the personnel; pre-testing of the questionnaire containing in the study protocol	*											
3. Purchase of supplies	*	*	*	*	*	*	*	*	*	*	*	*
4. Getting medications	*											
5. Clinical trial (intervention) & data collection		*	*	*	*	*	*	*	*	*	*	
6. Data entry & analysis				*			*			*		*
7. Quarterly preliminary data report to donor agency				*			*			*		
8. Final report to donor agency; preparing of scientific publications												*

* Activities will start after confirmation of funding

Appendix # 2

BUDGET PROPOSAL

Item	Quantity	Units (months/days)	1 Unit Cost	Total
FIXED EXPENSES				
Personnel				
CHSR Consultant (revision of the project)	1	8 days	$300.00	$2,400.00
Project Manager/Coordinator (full-time position)	1	12 months	$600.00	$7,200.00
Project Assistant/Clinical Resident/Surgeon (full-time position)	2	10 months	$300.00	$6,000.00
Treating physician (include taxes)		10 months	$10.00/patient *(incentives)*	$3,000.00
Endoscopist (include taxes)	2	10 months	$15.00/patient	$4,500.00 *(for 300 patients)*
Data Entry Analyst	2	15 days	$24.00	$720.00
Taxes and Fringe Benefits				
20% income tax (local salaries)				$3,264.00
4% pension tax employee (local salaries)				$652.80
15% pension tax employer (local salaries)				$2,448.00
9% fringe benefit (local staff)				$1,252.80
28% fringe benefit (US citizens)				$672.00
Subotal (fixed)				$32,109.60
Operating Costs*				
Diazepam (valium)	600	10 months	$2.00/100 tablets	$12.00
Laboratory costs	300	10 months	$20.00/patient	$6,000.00
Travel (taxi & bus fee)		12 months	$50.00	$600.00
Office supplies		12 months	$40.00	$480.00
Copying/documents/data forms		12 months	$25.00	$300.00
Subotal (fixed)				$7,392.00

Pantoprazole (protonix) and placebo will be provided by the pharmaceutical company: ***fixed – 300 tablets (40 mg) and 900 vials (40 mg) of pantoprazole (protonix); 300 tablets and 900 vials of placebo; ***reimbursable*** – 50 tablets (40 mg) and 150 vials (40 mg) of pantoprazole (protonix); 50 tablets and 150 vials of placebo

BUDGET PROPOSAL *(continued)*

Item	Quantity	Units (months/days)	1 Unit Cost	Total
REIMBURSABLE EXPENSES				
Endoscopist (include taxes)	2	10 months	$15.00/patient	$900.00 *(for 60 patients)*
Diazepam (valium)	100	10 months	$2.00/100 tablets	$2.00
Gastroenterologist/consultant (include taxes)	1	10 months	$5.00/ consultation	$500.00 *(for 100 patients)*
Ulcer treatment cost	100		$50.00/patient	$5,000.00
Report on scientific conference/meeting (travel & living expenses)				$3,000.00
Subotal (reimbursable)				$9,402.00
Grand subtotal				$48,903.60
Miscellaneous	5% of the grand subtotal			$2,445.18
TOTAL				$51,348.78
Administrative fee	36.5% of the total			$18,742.30
GRAND TOTAL				**$70,092.00** *(including **$9,402.00** reimb.)*

Appendix # 3

STUDY PROTOCOL

ID # ___ ___ ___

Setting (check one):

Clinical Hospital # 3 ❒❒❒

"Armenia" Republican Medical Center ❒❒❒

Case History #_____

Date of admission _____ _____ _____
month day year

Name _____ _____
Last Initials

Clinical Diagnosis_____
_____
_____
_____

Gender: Male ☐ Female ☐

Age (years)_____ **Date of birth** _____ _____ _____
month day year

Blood type_____ **Rh factor**_____

BMI (kg/m^2):_____

Family history of peptic ulcer disease: Yes ☐ No ☐

Antral atrophic gastritis: Yes ☐ No ☐

Rheumatoid arthritis: Yes ☐ No ☐

COPD: Yes ☐ No ☐

Hepatic cirrhosis: Yes ☐ No ☐

Chronic renal failure: Yes ☐ No ☐

Pancreatitis: Yes ☐ No ☐

Use of NSAID ***(within last 3 months during at least 7 days)*****:** Yes ☐ No ☐

Use of paracetamol (acetaminophen) ***(within last 3 months during at least 7 days)*****:**

Yes ☐ No ☐

Use of corticosteroids ***(within last 3 months during at least 7 days)*****:** Yes ☐ No ☐

Multiple Organ Dysfunction Score (MODS):

Organ	Grade 1	Grade 2	Grade 3
Pulmonary dysfunction*	ARDS score > 5	ARDS score > 9	ARDS score > 13
Renal dysfunction	Creatinine > 0.160 mmol/l	Creatinine > 0.220 mmol/l	Creatinine > 0.440 mmol/l
Hepatic dysfunction	Bilirubin > 34 mmol/l	Bilirubin > 68 mmol/l	Bilirubin > 136mmol/l
Cardiac dysfunction**	Minimal inotropes	Moderate inotropes	High inotropes
Haematologic dysfunction: platelet count	>= 100	60-90	< 60

*ARDS score – Acute Respiratory Distress Syndrome score= A + B + C + D + E

A. Pulmonary finding by X-ray:
- 0 = normal
- 1 = diffuse, mild intestinal markings
- 2 = diffuse, marked intestinal/airspace opacities
- 3 = diffuse, moderate airspace consolidation
- 4 = diffuse, severe airspace consolidation

B. Hypoxemia (PaO_2/FiO_2)
- 0 = > 250
- 1 = 175-250
- 2 = 125-174
- 3 = 80-124
- 4 = < 80

C. Minute ventilation (L/min)
- 0 = < 11
- 1 = 11-13
- 2 = 14-16
- 3 = 17-20
- 4 = > 20

D. PEEP (cm H_2O)
- 0 = < 6
- 1 = 6-9
- 2 = 10-13
- 3 = 14-17
- 4 = > 17

E. Static compliance (ml/cm H_2O)
- 0 = > 50
- 1 = 40-50
- 2 = 30-39
- 3 = 20-29
- 4 = < 20

**Cardiac index < 3.0 L/min/m^2 requiring inotropic support:
Minimal inotropes = dopamine or doputamine < 5 mg/kg/min
Moderate inotropes = dopamine or doputamine 5-15 mg/kg/min
High inotropes = higher doses of the above agents

Magnitude of Stress Associated With Selected Life Events – Social Readjustment Rating Scale (SRRS):

Relative Stressfulness	Life Event (exact point value)	Checking (check all that apply)
I. Very high	A. Death of spouse (4) B. Divorce (4) C. Marital separation (4) D. Death of a close family member (4)	A. ☐ B. ☐ C. ☐ D. ☐
I. Subtotal		
II. High	E. Major personal loss of health due to illness or injury (3) F. Marriage (3) G. Job loss (3) H. Retirement (3) I. Major loss of health of a close family member (3) J. Birth or adoption of children (3)	E. ☐ F. ☐ G. ☐ H. ☐ I. ☐ J. ☐
II. Subtotal		
III. Moderate	K. Assuming major debt (e.g. taking out mortgage) (2) L. Promotion or demotion at work (2) M. Child leaving home (2)	K. ☐ L. ☐ M. ☐
III. Subtotal		
IV. Low	N. Changing residence (1) O. Vacation (1) P. Major holiday (1)	N. ☐ O. ☐ P. ☐
IV. Subtotal		
TOTAL	*(sum of I, II, III, and IV subtotals)*	

Smoking status (check one):

- Current ❒❒□

start smoking_____ packs/day/week_____
(days/months/years ago)

- Former ❒❒□

start smoking_____ packs/day/week_____ quit smoking_____
(days/months/years ago) (days/months/years ago)

- Never ❒❒ □

Alcohol consumption (check one):

- Yes □

Days/week_____

Drinks/day_____

The following are considered as standard drinks:
Beer: one 12-ounce can or bottle
Table wine: 4-ounce glass of wine
Fortified wine: 2 ½- ounce glass
Spirits (80 proof): 1 ¼-ounce, straight or mixed
Spirits (100 proof): 1-ounce, straight or mixed

- No □

Coffee consumption (check one):

- Yes □

Cups/day_____

Cups/week_____

- No □

The level of physical activity:

Leisure-time physical activity (check one):

Active (exercise 30 minutes/day, 5-7 days/week) ❐☐

Moderate (exercise less than 30 minutes/day, 5 days/week) ❐☐

Sedentary (no planned physical activity) ❐☐ ❐

Work-time physical activity (check one):

Yes ☐ No ☐

Sweat, breathlessness, incomfort during the work-time physical activity Yes ☐ No ☐

Member of "PAROS": Yes ❐ ❐☐ No ❐❐☐

EGDS:

On admission: Yes ❐☐ No ❐ ☐

EGDS diagnosis:_____
_____
_____

1 tablet (5 mg) of Diazepam 45 min before EGDS: Yes ❐☐ ❐ No ❐❐☐

Local anesthesia (spray): Yes ❐☐ ❐ No ❐☐ ❐

Side effects:_____
_____
_____

On the 4th day after the surgery: Yes ❐☐ No ❐☐

EGDS diagnosis:_____
_____

1 tablet (5 mg) of Diazepam 45 min before EGDS: Yes ❐❐☐ No ❐❐☐

Local anesthesia (spray): Yes ❒❒□ No ❒❒□

Side effects:_____
_____
_____

***H. pylori* test** (check one):

Positive □

Negative □

PANTOPRAZOLE (PROTONIX):

1 tablet (40 mg) of pantoprazole (protonix) on the day before surgery at 8 p.m.:

Yes ❒□ ❒ No❒□ ❒

Side effects:_____
_____
_____

1 vial of intravenous pantoprazole (protonix) after the surgery at 8 p.m.:

Yes ❒□ ❒ No ❒□

Side effects:_____
_____
_____

1 vial of intravenous pantoprazole (protonix) on the 1st day after the surgery at 8 p.m.:

Yes ❒□ No ❒□ ❒

Side effects:_____
_____
_____

1 vial of intravenous pantoprazole (protonix) on the 2nd day after the surgery at 8 p.m.:

Yes ❒□ No ❒□

Side effects:_____
_____
_____

SURGERY:

Name of surgical operation_____
_____
_____

Duration: _____ _____
hours minutes

Primary surgeon:

Years of experience_____

Anesthesia (check one):

Intubation anesthesia with mechanical pulmonary ventilation ❒

Other type_____ ❒
name of anesthesia

Used anesthetics (medications and doses): _____
_____
_____
_____

Side-effects due to anesthesia: _____
_____
_____

Mechanical ventilation: _____ _____
hours minutes

Reoperation: Yes ❒❒□ No ❒❒□

***# of reoperations:*_____**

Reason(s) for reoperation (indicate separately each reoperation with its reason):

_____
_____
_____

Postoperative complications (indicate any):_____
_____
_____
_____

***# of postoperative complications:*_____**

Death: Yes □ No □

Causes of death (indicate any)**:**

_____
_____
_____
_____

Appendix # 4

American University of Armenia

Department of Public Health

Institutional Review Board/Committee on Human Research

CONSENT FORM TEMPLATE

CHR#

Title of Research Project: Gastroprotective medications in primary and secondary prevention of stress ulceration in adult patients undergoing cholecystectomy

A graduate student as part of his thesis project in the Master of Public Health Program at the American University of Armenia (AUA) is conducting a clinical study regarding stress ulceration prophylaxis in surgical patients. The purpose of the study is to assess whether gastroprotective medications administered within the perioperative period decrease the rate of stress ulceration and the rate of stress ulcer complications in adult patients undergoing cholecystectomy.

Your participation in the study will be limited within the course of hospitalization.

We appreciate your participation in this study, which is highly valuable for us.

PROCEDURES

All patients will be divided into two groups (experimental and control) by drawing a card indicating to which group a patient would be assigned. All patients will be thoroughly examined before and after the surgery and will be asked several questions to determine possible baseline variables. All patients will undergo a gastroscopy on admission and on the 4^{th} day after the

surgery. The purpose of this procedure is to determine the presence or absence of ulceration. A gastroscopy is a medical procedure, which is performed using a thin, flexible gastroscope (tube) under the local anesthesia (spray) of the mouth and throat. In addition, for anesthetic purposes, before the procedure all patients will be administered an oral medication, diazepam, which will make the procedure more comfortable. This procedure is needed to complete an assessment of patients before and after surgery.

Patients in the experimental group will receive a gastroprotective medication, pantoprazole (protonix), before and after the surgery. On the day before surgery, at 8 p.m. he/she will receive 1 tablet of the medication. In addition, on the day of the surgery and 2 following days afterward, once daily, at 8 p.m. he/she will receive intravenous pantoprazole (protonix) administered through the intravenous tubing already in place for the anesthesia. So, no additional injection will be made. Patients in the control group will receive placebo, i.e. an inert harmless substance that looks, tastes, and smells like the medication (pantoprazole), but has no medical influence on the organism, in the regime and formulation similar to experimental group.

RISK/DISCOMFORT

Gastroscopy (with or without biopsy) is a procedure used at the discretion of the physician for the preoperative assessment of patients undergoing upper abdominal surgery. According to the medical literature and clinical practice, the risk of developing side effects due to a gastroscopy is very low. Likewise, pantoprazole (protonix) is very well tolerated and has been shown to be significantly superior in safety then other antacid medications. In rare cases the literature demonstrates minimal side effects like headaches or itching.

AUA does not have a program to provide compensation for any injuries or bad effects, which are a consequence of your routine surgical experiences.

BENEFITS

You will *benefit* from the participation. The following benefits should be considered. If during the preoperative gastroscopy peptic ulcer disease and/or gastric/duodenal erosions had been detected, you will be excluded from the study and will be provided a free of charge consultation regarding your illness and $50 for the course of treatment. If you will develop stress ulceration or its complications (bleeding), you will be provided a free of charge consultation regarding your illness and $50 for the course of treatment prescribed by the qualified gastroenterologist/surgeon/ICU specialist. Also, the investigator will cover the cost of laboratory analyses. In addition, the potential health benefit of the study is a thorough examination, which could lead to more exact and comprehensive preparation for the surgery.

CONFIDENTIALITY

Your name and address or other identifying data will be confidential. The data you provided during the assessment by the physician will be accessible only to you medical staff and to the Public Health Department of the AUA.

VOLUTARINESS

It is your decision whether to participate in the study or not. You can stop being in this study at any time. You can withdraw from the study at any time without prejudice to future

medical care. Your participation may be terminated also by the investigator if it is determined you are not a good candidate for continuing in the study.

WHOM TO CONTACT:

You should ask the person in charge listed below any questions you may have about this research study. You should ask him/her questions in the future if you do not understand something about the study. The researchers will tell you anything new they learn that they think will affect you.

If you want to talk to anyone about this research study you should call the person in charge of the study, **[Michael Thompson]** at **[phone number: (3741) 512592 and/or e-mail: mthompso@aua.am]**. The person in charge of the study will answer your questions.

If you want to talk to anyone about the research study because you feel you have not been treated fairly or think you have been hurt by joining the study you should contact the American University of Armenia at (3741) 512512

If you agree to be in this study, please sign your name below.

_____

Subject's signature (including children, when applicable)

_Witness to Consent Procedures*

_____

Signature of Investigator

Date

CHRNo.

* Optional unless subject is illiterate, or unable to *sign.*

Note: Signed copies of this cogent form must be a) retained on file by the Principal Investigator, b) given to the participant, and c) put in the patient's medical records (when applicable).