12-1-2019

Systematic Review: Enhanced Recovery After Cholecystectomy Surgery

Meghan Cole

SYSTEMATIC REVIEW:

ENHANCED RECOVERY AFTER CHOLECYSTECTOMY SURGERY

A Major Paper

by

Meghan Cole

Approved:

Committee Chairperson _____ _____
(Date)

Committee Members _____ _____
(Date)

_____ _____
(Date)

Director of Master's Program _____ _____
(Date)

Dean, School of Nursing _____ _____
(Date)

SYSTEMATIC REVIEW:

ENHANCED RECOVERY AFTER CHOLECYSTECTOMY SURGERY

by

Meghan Cole

A Major Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Nursing

in

The School of Nursing

Rhode Island College

2019

Abstract

This systematic review aimed to answer the clinical question, which perioperative enhanced recovery after surgery (ERAS) techniques are most effective in decreasing recovery time and length of stay for adults, aged 18-65, undergoing cholecystectomy surgery? In an effort to curb healthcare spending, ERAS is one way to reduce hospital-associated costs. Originally developed in Denmark, ERAS is a patient-centered initiative that aims to reduce the body's stress response, leading to improved patient outcomes and decreased hospital lengths of stay. Betty Neuman's Systems Model was used as a theoretical framework to enrich the understanding of enhanced recovery and how it works to improve patient care.

This review followed the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) checklist. Using the PRISMA guidelines, current literature was systematically searched to select randomized controlled trials in a consistent, repeatable way. Data from the studies were collected, analyzed, evaluated, and reported in the same manner, using charts to organize data clearly. The following search terms were entered into the Cochrane database, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), CINAHL Plus with Full Text, PubMed, PubMed Health, and MEDLINE: "ERAS," "enhanced recovery," "fast-track surgery," "fast-track rehabilitation," and "cholecystectomy."

Four randomized-controlled trials met inclusion and exclusion criteria. The findings of the cross-study analysis determined that utilizing TIVA (with propofol and remifentanil) and/or including a 20% mannitol infusion pre-induction are two ERAS techniques that may lead to improved recovery times and shorter lengths of stay for patients undergoing laparoscopic cholecystectomy surgeries.

Acknowledgements

To my family and friends- for supporting me throughout this writing process. Special thanks to my incredibly supportive husband. I love you so much and could not have done this without you!

Table of Contents

SYSTEMATIC REVIEW: ENHANCED RECOVERY AFTER CHOLECYSTECTOMY SURGERY

Background/Statement of the Problem

In order to understand the importance of enhanced recovery, one first needs to look at the health care system as a whole. Healthcare costs are a major issue in today's economy. With an aging population and less-than-efficient medical practices, these costs only continue to rise. The centers for Medicare and Medicaid Services reported an increase of 5.8% in national health expenditure in 2015, now accounting for 17.8% of gross domestic product. Increased spending is expected each year through 2025 at an average rate of 5.6% per year. In 2015, hospital care accounted for 38.3% of health spending and the working-age group was responsible for 54% of the overall expenditure, though they made up 61% of the population (NHE Fact Sheet, 2017). Complications related to surgery, long ICU stays, long overall hospital visits, as well as many other factors all contribute to these high healthcare costs.

There are many potential ways to lower spending and cut back healthcare costs. As stated above, hospital costs make up almost 40% of health spending, the most of any category, making this is a natural place to start looking for solutions. Some suggestions include methods to rapidly identify and treat infections (Perez et al., 2013), incorporating newer, more cost-efficient procedures, eliminating wasteful practices, decreasing length of stay and using standardized methods and best practices to improve outcomes and their implementations (Sahni, Chigurupati, Kocher, & Cutler 2017). While not all of these methods are necessarily appropriate or timely ways to decrease costs, there are a few that do not require additional resources. Providing standardized, yet patient-specific care can

lead to faster recovery times and decreased lengths of stay, therefore decreasing overall costs. The need for this kind of patient-centered care is what led to the development of enhanced recovery after surgery programs.

Enhanced recovery after surgery, or ERAS, is an initiative that aims to improve patient outcomes, and decrease hospital lengths of stay by decreasing the body's stress response (Enhanced Recovery Partnership Programme, 2010). It was originally developed in Denmark and has now spread through most parts of Europe and the Americas. Various elements of the program include the following:

- pre-admission counseling,
- no bowel prep,
- fluid and carbohydrate loading,
- no fasting, no premedication,
- no nasogastric tubes,
- mid-thoracic epidural anesthesia/analgesia,
- short-acting anesthetic agents,
- avoidance of sodium and fluid overload,
- short incisions, no drains,
- warm air body heating in the operating room,
- routine mobilization care pathway,
- non-opiate oral analgesics/NSAIDs,
- prevention of nausea and vomiting,
- stimulation of gut motility,

- early removal of catheters,
- perioperative oral nutrition, and
- auditing of compliance/outcomes (Fearon et al., 2005).

While these elements are at least somewhat evidence-based, not all of the evidence is thorough or even consistent. Cholecystectomies are a common same day general surgery, so they are a good model surgery to use in order to study various enhanced recovery implementations. For that reason, the purpose of this major paper is to complete a systematic review of current literature, in order to answer the clinical question, which perioperative ERAS techniques are most effective in decreasing recovery time and length of stay for adults, aged 18-65, undergoing cholecystectomy surgery?

Theoretical Framework

Using nursing theory to help guide and shape a research study contributes to the depth and meaning of the work. In this study, Betty Neuman's Systems Model is used to guide the understanding of enhanced recovery after surgery as well as to help develop best practices from the aggregated studies. In the following section, a review and brief evaluation of this model will be conducted, followed by a discussion on implications to both anesthesia as well as evidence-based practice.

Neuman's model started out as a guide used to teach her students how to treat a patient as a whole when providing nursing care (Neuman & Fawcett, 2002). The model was meant to be a guide for understanding the parts of man and how to influence them. Her first published version was in 1972, though the diagram itself was copyrighted in 1970. Her theory has been continuously studied, critiqued, and refined for almost 50 years (Neuman & Fawcett, 2002).

The Neuman Systems model is rooted in systems theory, which aims to systematically organize complex elements that interact with each other (Neuman & Fawcett, 2002). Since nursing is a large and complex field that continues to grow, a systematic approach for organizing nursing concepts is not only appropriate, but also quite useful. Neuman describes her model as, "… an open systems model that views nursing as being primarily concerned with defining appropriate action[s] in stress-related situations or in possible reactions of the client/client system" (Neuman & Fawcett, 2002, p.12). She also wrote that in this model, "the client is viewed as a composite of interacting variables- physiological, psychological, developmental, sociocultural, and spiritual- that are, ideally, functioning harmoniously or are stable in relation to both

internal and external environmental stressor influences" (p. 31). This statement shows that the client's wellness must be assessed on multiple variables and also points to several other assumptions of the theory. Summaries of the model's assumptions are described below, in Box 1. These assumptions were consistent throughout the theory's text and tools, contributing to the clarity of the model.

The purpose of Neuman's System Model is prescriptive- i.e. what interventions should be done to achieve prescribed goals (Polit & Beck, 2017). It is a grand theory, encompassing nearly every aspect of nursing in any given setting (Neuman & Fawcett, 2002). It has transferability to many other healthcare disciplines as well, making it quite broad in scope. Even though it is a grand theory with many concepts, the model defines them clearly as shown in Table A-1, found at the end of this review. Neuman's original diagram helps further illustrate definitions and how components are connected within the theory. In the full publication, this diagram, along with many others, aid to further clarify the conceptual definitions (Neuman & Fawcett, 2002). These concepts are not operationally defined, however, as defining them in this way would narrow the applicability of this theory. Additionally, because the model is systematic in nature, the organization of concepts is logical, though the breadth of the model can sometimes make them hard to follow. These concepts are consistent throughout the explanation of the model though, providing a solid foundation for understanding. Theory analysis suggests this theory has thoroughly defined concepts and components, it is consistent in its use of definitions, and it is described in a logical way. In addition to analyzing Betty Neuman's theory, it is also important to evaluate it.

Box 1. Neuman Systems Model: Assumptive Statements

- "Each individual client or group as a client system is unique; each system is a composite of common known factors or innate characteristics within a normal, given range of response contained within a basic structure."
- "The client as a system is in dynamic, constant energy exchange with the environment."
- "Many known, unknown, and universal environmental stressors exist. Each differs in its potential for disturbing a client's usual stability level, or normal line of defense. The particular interrelationships of client variables- physiological, psychological, sociocultural, developmental, and spiritual- at any point in time can affect the degree to which a client is protected by the flexible line of defense against possible reaction to a single stressor or combination of stressors."
- "Each individual client/client system has evolved a normal range of response to the environment that is referred to as the normal line of defense, or usual wellness/stability state. It represents change over time through coping with diverse stress encounters. The normal line of defense can be used as a standard from which to measure health deviation."
- "When the cushioning, accordianlike effect of the flexible line of defense is no longer capable of protecting the client/client system against an environmental stressor, the stressor breaks through the normal line of defense. The interrelationships of variables- physiological, psychological, sociocultural, developmental, and spiritual- determine the nature and degree of system reaction or possible reaction to the stressor."
- "The client, whether in a state of wellness or illness, is a dynamic composite of the interrelationships of variables- physiological, psychological, sociocultural, developmental, and spiritual. Wellness is on a continuum of available energy to support the system in an optimal state of system stability."
- "Implicit within each client system are internal resistance factors known as lines of resistance, which function to stabilize and return the client to the usual wellness state (normal line of defense) or possibly to a higher level of stability following an environmental stressor reaction."
- "Primary prevention relates to general knowledge that is applied in client assessment and intervention in identification and reduction or mitigation of possible or actual risk factors associated with environmental stressors to prevent possible reaction. The goal of health promotion is included in primary prevention."
- "Secondary prevention relates to symptomatology following a reaction to stressors, appropriate ranking of intervention priorities, and treatment to reduce their noxious effects."
- "Tertiary prevention relates to the adjustive processes taking place as reconstitution begins and maintenance factors move the client back in a circular manner toward primary prevention."

(Neuman & Fawcett, 2002, p. 14)

Components of theory evaluation include determining simplicity and clarity, usefulness, testability, generalizability, and significance (McEwen & Wills, 2014). This model is both very broad, as well as complex, so it is not considered to have parsimony. However, it is clear and detailed in its definitions. As a grand theory that has been developed for nearly 50 years, there are many uses that have been studied as well. The published model also provides systematic reviews of its use in various settings including clinical practice, nursing research, nursing education, and nursing administration, with several reviews and tools discussed under each section (Neuman & Fawcett, 2002). Many articles have used the Neuman System Model to determine best practices in different nursing fields, making it very useful for determining and implementing evidence-based practice, or EBP (Neuman & Fawcett, 2002). Because it takes into account the whole patient in a systematic way, this model lends itself well for use in developing EBP guidelines. In the recent few editions of the published model, assessment and intervention tools were published to aid in using this theory in practice. By doing so, the theory is more testable empirically and real-world applications can be seen more easily. As this theory is a broad systems theory, it is applicable to most other healthcare fields. The Neuman Systems Model has been used in fields such as medicine, physical and occupational therapies, education, psychology, and oncology, just to name a few (Neuman & Fawcett, 2002). Even specific tools for different fields have been developed from this theory, making it very generalizable. Finally, as this theory is useful, broad, well-tested and studied, it has a great deal of clinical significance, particularly to the field of nursing. It is not only relevant here in the United States, but is broad enough to encompass geographical, sociological, and cultural differences as well.

The Neuman Systems Model is not only applicable to research and nursing in general, but more specifically to the research and practice of nurse anesthesia. Martin (1996) shows how the practice of anesthesia could incorporate the Neuman Systems Model. The author suggests that as the CRNA is providing peri-operative anesthesia care, they are actually supporting the normal line of defense of the client as well. By impeding the stressors the client may experience, nurse anesthetists are using multi-level prevention techniques to help the patient achieve and maintain a homeostatic balance (Martin, 1996). Ume-Nwagbo, DeWan, and Lowry (2006) provide two case examples to illustrate the use of the model as a theoretical framework for determining best practices. They used the model to assess individual and family needs, as well as to develop a plan to deliver care in a respectful and knowledgeable way, honoring the client system. The model was a great choice for this work because it allowed the researchers to understand the whole client in regards to all five client variables, and to understand that each client will respond differently. This allowed the researchers to anticipate and prevent client responses to stressors with different levels of prevention (Ume-Nwagbo, DeWan, & Lowry, 2006). These articles demonstrate how Neuman's System Model can be used in different settings and for different purposes, but always to support the client and assist in lessening the response to environmental stressors.

Betty Neuman's Systems Model is well-studied theory that helps organize and explain many aspects of nursing. In its breadth, this model will do two things to assist in the understanding and organization of this review. First, it will give deeper meaning to the techniques used in ERAS protocols, as they are standardized, yet patient-specific. These protocols were developed specifically to reduce the stress-response experienced by

the patient due to the surgery they received (Enhanced Recovery Partnership Programme, 2010). The Neuman Systems Model looks at what environmental stressors are affecting the client as a whole, and determines which interventions are appropriate to reduce their specific stress-related response (Neuman & Fawcett, 2002). This leads to the second use for this review- the model lends itself well to developing evidence-based practice. The tools included as well as the concepts themselves, force the evaluator to look at every aspect of the patient and determine holistically, which interventions are most appropriate to reduce their stress response by strengthening patients lines of resistance and defense. For this review, the Neuman Systems Model is used as a guiding theoretical framework to provide deeper meaning and understanding of ERAS protocols, their implementations, as well as their outcomes in adults undergoing cholecystectomy surgery. The following literature review will further define the concepts of physiologic stress, the surgical stress response, and how ERAS can play a role in mitigating those responses.

Literature Review

Cochrane, CINAHL Plus, Pubmed, and Medline databases were searched. Search terms were applied both independently and in combination, which included: physiologic stress, surgical stress, stress response, enhanced recovery, ERAS, and fast-track surgery. Studies published between 2000-2018 were included in the search. Additionally, seminal works that were published as early as the 1950s were included, as they are vital to our current understanding of the surgical stress response. The following literature review summarizes what the stress response is, how that differs from the surgical stress response, and what current ERAS literature recommends is the best way to attenuate those responses in order to recover a patient efficiently.

Stress and the body

Stress comes in many different forms and from a variety of causes. As early as 1970, Clarke determined that the magnitude of a stressor affects the response. In his study, Clarke compared serum glucose levels in patients under different anesthetic techniques for a variety of procedures and found that the rises in stress-induced blood glucose levels were proportional to the amount of stimulus implemented. Smaller stimuli led to smaller increases in blood glucose, when compared to larger stimuli. The term ‘stress’ tends to have a negative connotation, but there is also good stress, or eustress, that results in a positive stress response. Additionally, many other variables influence how and to what degree a stress response is elicited (Greenberg, Carr, & Summers, 2002). Neuman describes stressors as “environmental factors that are intra-, inter-, and extrapersonal in nature and have the potential for disrupting system stability by

penetrating the system lines of defense and resistance. Their outcome may be either positive or negative" (Neuman & Fawcett, 2002, pg. 322-324). In other words, a stressor is a true or perceived threat to a person's homeostatic balance. Stressors can come from all kinds of sources, including physiological, psychological, sociocultural, developmental, and even spiritual sources (Neuman & Fawcett, 2002). The following section will discuss the stress response, with a focus on the biological, or physiological, components.

The Stress Response. Over the years of stress-related research, several components have emerged as mechanisms involved in the stress response. Cuthbertson (1932) demonstrated that after a stressful stimulus, in this case limb injury, the body showed manifestations of increased catabolism. Temperature in all case studies published rose one to two degrees Celsius within the first 48 hours of injury and lasted for one to two days. Additionally, by graphically displaying the collected data, Cuthbertson was able to determine that oxygen consumption increased in the days following injury, and in a similar fashion, nitrogen excretion increased as well (Cuthbertson, 1932). Together, these changes are indicative of increased catabolism. Further observations by Selye (1956) illustrated that the body's reaction to stress is an adaptive response that allows the individual to compensate for the disruption in homeostasis. Two components in particular make the response adaptive. The first component is that the body mobilizes energy, i.e. catabolism. The second is that "a new pattern of energy distribution emerges" (Schneiderman, Ironson, & Siegel, 2005, pg. 5). Energy is redistributed to the tissues that become more active upon initiation of the stress response. Skeletal muscles and the brain receive increased amounts of the newly mobilized energy to support a "fight or flight"

stress response. In an acute stress response, the immune system also activates and mobilizes cells, readying the body to respond to a biological or physical invasion (Schneiderman et al., 2005). While these short term effects are intended to aid the body in battling an acutely stressful situation, if the threat persists or is extremely severe, the continued stress response can have deleterious effects on the body that can ultimately damage health, especially in those that are more vulnerable (i.e. children, older adults, & individuals with many co-morbidities) (Schneiderman et al., 2005).

The Stress System. Tsigos, Kyrou, Kassi, and Chrousos (2016) comprehensively discuss the stress response and help to define 'the stress system'. These authors point out that although the entire central nervous system (CNS) is involved to some degree in the maintenance of homeostasis, certain areas of the brain have key roles in the stress response. The main components can be found in the hypothalamus and brain stem. They include, but are not limited to, the parvocellular corticotropin-releasing hormone (CRH) as well as arginine-vasopressin (AVP) neurons, found within the hypothalamus, the CRH neurons in the medulla, as well as the locus coeruleus (LC), norepinephrine (NE)-synthesizing cells, and other catecholaminergic cell groups of the medulla and pons. These components, along with their peripheral counterparts, make up the hypothalamic-pituitary-adrenal (HPA) axis, a crucial component in the stress system. A separate circuit, consisting of stimulatory and inhibitory networks as well as multiple sites for peripheral interactions, forms a physiologic system within the CNS that leads to activation of the stress system. The activating circuit stimulates both the sympathetic nervous system (SNS) as well as the HPA axis, and it is the interactions between these components that allow the body to modulate the adaptive stress response (Tsigos et al., 2016).

Hypothalamic-pituitary-adrenal axis. In order to fully understand how CRH, AVP, and other necessary components lead to the adaptive response to stress, one needs to understand how the HPA axis works. The integrity and regulation of the HPA axis is crucial to the stress response. CRH is the primary regulator of adrenocorticotropic hormone (ACTH) secretion by the anterior pituitary, with AVP acting as a potent synergistic factor (Tsigos et al., 2016). After secretion by the anterior pituitary, ACTH travels to its target organ, the adrenal glands. ACTH is a critical regulator of glucocorticoids (i.e. cortisol) and adrenal androgen secretion and may also help regulate aldosterone. Glucocorticoids are the final effectors of the HPA axis. They act on intracellular receptors found throughout the entire body and can produce a wide range of effects. Actions of glucocorticoids include trans-activating or trans-repressing appropriate hormone-response genes, altering the electrical potential of neurons, regulating mitochondrial functions and energy metabolism, influencing the secretion rates of certain proteins, as well as regulating the HPA axis and terminating the stress response (Tsigos et al., 2016).

Sympathetic nervous system. In addition to HPA axis involvement, the sympathetic nervous system also plays a large role in the stress response. The SNS, along with the parasympathetic nervous system (PNS) are branches of the autonomic nervous system (ANS). The SNS provides a rapid mechanism to control the response to stress, also known as the flight or fight response (Tsigos et al., 2016). The SNS and PNS often work hand in hand to stimulate or suppress various functions of the body. Innervation of peripheral organs is via bilateral chains of sympathetic ganglia that synapse with neurons that innervate smooth muscle of the vasculature, skeletal muscles, the heart, kidneys, gut,

adipose tissue, and many other organs/tissues. Additionally, sympathetic impulses can act on the adrenal medulla, leading to the secretion of epinephrine and norepinephrine as well. These actions culminate and lead to increased blood pressure, contractility and heart rate, and it also prepares the body to act quickly, whether it be to fight or run (Tsigos et al., 2016).

The surgical stress response

Not only does the body experience threats to homeostasis, it also has specific responses to surgical procedures. According to Betty Neuman, surgery would certainly be classified as a stressor, as it disrupts the stability and homeostasis of multiple systems (Neuman & Fawcett, 2002). The surgical stress response has been studied since the early 1900s, as well as ways to mitigate the effects of the stress response during and after surgery.

Historical discoveries. Cannon (1915) was one of the first scientists studying stress to write a research text about it. The text contained research summaries from the previous 40 years, as well as his own empirical evidence evaluating the body's response to pain, hunger, fear, and rage. One experiment Cannon conducted involved placement of a tube in the throat of animals without anesthesia. The intense physical pain these animals experienced was associated with elevated urine glucose values. Testing urine for stress-related chemicals was a commonly used method to determine the human response to surgery. It wasn't until decades later, when Hine et al. (1976) determined that plasma concentrations of catecholamines (adrenaline and noradrenaline) provided a more accurate reflection of the stress response. His research appraised catecholamine

concentrations before, during, and after cardiopulmonary bypass. He found that plasma concentrations of both adrenaline and noradrenaline increased with bypass, averaging 0.42 mcg/L adrenaline and 0.28 mcg/L noradrenaline before bypass, increasing to 0.94 mcg/L adrenaline and 0.78 mcg/L noradrenaline during bypass, and then backing off to 0.67 mcg/L adrenaline and 0.58 mcg/L noradrenaline after completion of bypass (Hine et al., 1976). Previous bypass data showed little to no change in catecholamine levels during bypass when measured using urinalysis, showing that alternative methods of analysis, such as assessing plasma concentrations, were therefore needed to determine the significance of stress on the body during surgery (Hine et al., 1976). By applying these findings, Pickar, Cohen and Dubois (1983) found that plasma levels of beta-endorphin as well as cortisol were significantly increased after abdominal surgery. ($p = 0.01$). Moreover, they determined that there was an inverse relationship between plasma levels of these substances and the amount of analgesia, in this case morphine, required post-operatively ($p = 0.01$).

Elevated levels of cortisol and endorphins are not the only way to determine the existence of a stress response. Gaubatz and Wehner (1991) focused their research on the physiological changes associated with stress and how to attenuate them. In this study, doses of esmolol, fentanyl, or a combination of both were used to blunt the adrenergic physiological response to laryngoscopy during induction of anesthesia in 44 patients. Patients were randomly divided into four groups to receive one of the following: esmolol 1mg/kg with fentanyl 2mcg/kg, esmolol 1 mg/kg alone, fentanyl 3.5 mcg/kg alone, or placebo (control). The results showed that the patients treated with fentanyl were significantly less responsive to the effects of intubation than those not receiving fentanyl

($p < 0.001$) in terms of SBP, DBP, and MAP. Additionally, heart rate increases were less when esmolol was used ($p < 0.05$) Therefore, the stress response was attenuated the most in patients who received doses of both medications (Gaubatz & Wehner, 1991). The research from the past century demonstrates that there is in fact a stress response to surgery, there are supported methods to attenuate that response, and the methods for doing so are continuously changing.

Desborough (2000) conducted a thorough review of surgical stress to date. He found that the surgical stress response is not largely different from the generic stress response, as it too activates the sympathetic nervous system and is characterized by an increase in pituitary hormone secretion. The SNS is activated by the hypothalamus during the surgical stress response. SNS activation leads to an increase in catecholamine secretion from the adrenal medulla (adrenergic response), namely norepinephrine and epinephrine (Desborough, 2000). Additionally, surgical stress is so significant that it can cause a mass discharge of catecholamines when large portions of the SNS are all discharge simultaneously, increasing the body's ability to participate in the fight or flight response.

Endocrine activation is also stimulated by the hypothalamus via releasing factors. The anterior pituitary synthesizes and releases increased amounts of ACTH, growth hormone (GH), and prolactin (PRL) in response to a surgical stimulus (Desborough, 2000). While the levels of ACTH, GH, and PRL increase, levels of other anterior pituitary hormones, including thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) remain relatively stable upon surgical stimulation. The posterior pituitary produces increased arginine vasopressin which acts as

an anti-diuretic hormone as well as synergistically stimulating the release of ACTH from the anterior pituitary (Desborough, 2000).

Triggering the surgical stress response.

Egdahl (1959) studied trauma in both the innervated and denervated extremities of dogs to determine if a "wound hormone" existed, triggering a stress response. While he did not find enough evidence to support his claim at the time, his research helped lead to the discovery of cytokines. It is believed that cytokines are a key activator involved in this process. According to Desborough (2000), an early response to tissue injury involves activated immune cells, including leukocytes and fibroblasts, producing cytokines in order to mediate the immune and inflammatory responses. Hall's medical text now describes cytokines as small proteins that act like hormones as part of the immune system's response to insult or injury (Hall & Guyton, 2016).

The acute phase response. The acute phase response involves the changes that occur in the body in response to tissue injury. It initiates the stress response by stimulating the hypothalamus via an afferent sensory signal from the site of injury, or surgery (Desborough, 2000). Surgery causes the release of specific cytokines: interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). IL-1 and TNF-α are released immediately upon tissue damage and they stimulate the production of IL-6, which is the main cytokine responsible for the acute phase response according to Desborough (2000).

Another major component of the acute phase response involves the liver. The liver decreases its production of some proteins, such as albumin and transferrin, in order

to produce acute phase proteins, including C-reactive protein (CRP), fibrinogen, and α_2-macroglobulin (Desborough, 2000). These proteins act as inflammatory mediators, scavengers in tissue repair, and they are responsible for the changes that occur to produce IL-6. IL-1 and IL-6 can both stimulate the pituitary to release higher levels of ACTH, stimulating or potentiating the stress response. In studies that compared the stress response in laparoscopic surgery versus open surgery, the stress response was not greatly reduced due to lesser surgical trauma, in spite of finding the concentrations of injury-related proteins to be lower in laparoscopic procedures. It is suggested therefore, that stimuli for the stress response arise from a combination of afferent nerve fibers from visceral and peritoneal sources, as well as from the abdominal wall itself (Desborough, 2000). To further support this, Jurczok, Zacharias, Wagner, Hamza & Paolo (2007) studied the systemic response in laparosopic versus open radical prostatectomy. They found an increase in IL-6 and CRP postoperatively in both types of surgery, but there was no significant difference in serum levels between the two.

Implications for intra-operative anesthesia management.

The surgical stress response has implications for the intra-operative period, particularly for the anesthesia provider. First, it is important for the provider to understand the stress response, in order to anticipate, prevent and mitigate those changes as much as possible during surgery. Various pharmacological agents have been studied to determine their role in reducing the stress response. The following table summarizes the effects of opioids, propofol, etomidate, benzodiazepines, clonidine, and regional anesthesia techniques on the surgical stress response.

Table 1. Effects of pharmacological agents

Pharmacologic agent	Effect on stress response
Opioids	Suppresses HPA axis in humans at the hypothalamic level Morphine: suppresses release of corticotropin, leading to lower levels of cortisol; blocks secretion of GH
Propofol	Induction dose will suppress circulating cortisol, though it does not prevent secretion; deep or prolonged anesthesia doses will completely eliminate circulating cortisol
Etomidate	Interferes with steroid production by inhibiting the enzymes responsible; blocks production of aldosterone and cortisol for 6-12 hours after a single induction dose
Benzodiazepines	Lessens the cortisol responses to surgery in the abdomen and periphery; site of action is at the hypothalamic-pituitary level
Clonidine	Centrally-acting anti-hypertensive (α2-agonist); produces sympatholytic activity, leading to improved hemodynamic stability; also lessens anesthesia and analgesia requirements
Regional anesthesia	Epidurals with extensive use of local anesthetics will prevent the endocrine and metabolic responses to surgeries in the pelvis and lower limbs; blocks afferent input to the hypothalamus and efferent output to the autonomic neural pathway, preventing adrenocortical and glycemic responses to surgical stress

(Desborough, 2000, pgs 113-115; Paola et al., 2015)

Post-operative clinical consequences.

The culmination of the surgical stress response has an array of postoperative clinical consequences on the body. Cuthbertson (1932) observed that there is a 2-phase metabolic response that involves an initial "ebb" phase, followed by a "flow" phase after. The initial ebb phase begins a few hours after surgery and persists for 48-72 hours, wherein metabolic activity is decreased. The flow phase starts after the ebb phase and lasts for days to weeks, depending on the injury type and severity and is a period of increased metabolic activity (Cuthbertson, 1932). Researchers have since studied these responses in further detail. Moore (1953) confirmed a state of decreased metabolism following surgery in his observational studies of the surgical stress response. He found

that the body was excreting higher levels of nitrogen, potassium, body fat, and water the first three to four days postoperatively, as they were not being used metabolically. In the days after that (post-operative days five to eight), Moore found that there were decreased amounts of potassium and nitrogen excreted, and increased amounts of sodium, suggesting the body is increasing its metabolic functioning during that time (Moore, 1953).

Studies since the 1950s continue to confirm these findings. In the last decade, researchers have been able to determine other physiological differences associated with post-operative changes in the body. Finnerty, Mabvuure, Ali, Kozar, and Herndon (2013) determined physiological responses in the first phase to include reduced cardiac output, reduced oxygen consumption, reduced basal metabolic rate, and reduced glucose tolerance (Finnerty et al., 2013). Phase II responses include increased cardiac output, increased respiratory rate, increased oxygen consumption, hyperglycemia, hypermetabolism, increased skeletal muscle breakdown, and a negative nitrogen balance (Finnerty et al., 2013). The hypermetabolism response is partially due to increased levels of catecholamines and affects carbohydrates, proteins, and fats. With the addition of the heightened inflammatory response, these changes can lead to organ failure. To lessen these responses, nutritional and pharmacological interventions have been studied to determine the most effective ways to improve patient outcomes. Due to the different phases involved in the response, dynamic interventions are needed to meet the patient's varying metabolic needs.

Enhanced Recovery After Surgery

Enhanced recovery after surgery, or ERAS, is an initiative that aims to improve patient outcomes, and decrease hospital lengths of stay by decreasing the body's stress response to surgery (Enhanced Recovery Partnership Programme, 2010). It was originally developed in Denmark and has now spread through most parts of Europe and the Americas. Different elements of the program include pre-admission counseling, no bowel prep, fluid and carbohydrate loading, no fasting, no premedication, no nasogastric tubes, mid-thoracic epidural anesthesia/analgesia, short-acting anesthetic agents, avoidance of sodium and fluid overload, short incisions, no drains, warm air body heating in the operating room, routine mobilization care pathway, non-opiate oral analgesics/NSAIDs, prevention of nausea and vomiting, stimulation of gut motility, early removal of catheters, perioperative oral nutrition, and auditing of compliance/outcomes (Fearon et al., 2005). While these elements are at least somewhat evidence-based, not all of the evidence is thorough or even consistent.

Empirical Evidence in Support of ERAS protocols.

There are many ERAS elements that have been well studied and implemented. Thus far, research has been conducted in several perioperative surgical areas including colorectal, gynecological, orthopedic, and cardiac. In a randomized control trial, conducted by Abdikarim et al. (2015) authors aimed to evaluate the safety and efficacy of ERAS programs in patients undergoing laparoscopic radical gastrectomy for stomach carcinomas. Sixty-one participants were recruited and then randomly assigned into the two groups (Abdikarim et al., 2015). The ERAS group had 30 participants and the control group had 31, though neither group was blinded. Apart from the ERAS interventions,

which included no fasting, no bowel prep, no drainage or NG tubes, restricted IV fluids, and early mobilization, the two groups received the same surgical procedure (Abdikarim et al., 2015). The ERAS group showed statistically significant improvements over the control group on every measure. Average time to ambulation was 2.6 days compared to 3.1 ($p = 0.04$); average time to defecation was 3.1 days compared to 3.6 ($p = 0.01$); average time to food intake was 2.9 days compared to 3.5 ($p = 0.003$); and length of stay was 6.8 days compared to 7.7 ($p = 0.002$). The sample size was small, mainly male (2:1 ratio), and not necessarily racially diverse, making generalizability limited (Abdikarim et al., 2015). Overall, this study supported the use of ERAS protocols in laparoscopic radical gastrectomies as a safe and more effective alternative to traditional care.

In a similar study by Liang et al. (2016), investigators compared a group who received the ERAS protocol versus a control group receiving standard care in laparoscopic hepatectomy procedures. The ERAS group received interventions such as pre-operative education, no bowel preparation, no fasting, carbohydrate loading prior to surgery, fewer abdominal drains, less IV fluids, addition of local anesthesia, thorough pain control, early advancement of diet and early mobilization. The sample included 187 participants who were randomized and blinded into two groups. There were 80 participants in the ERAS protocol and 107 in the control group. Pain scores were obtained using a visual analog scale, ranging from zero to ten. The results showed that pain scores were significantly lower in the ERAS group on postoperative day one (an average score of 1.9 versus 2.6, $p = 0.001$), day three (average score of 1.3 versus 2.4, $p = 0.001$), and day five (average pain score of 0.8 versus 1.8, $p = 0.001$). The ERAS group also advanced their diet faster (1.7 days versus 4.5, $p = 0.001$); post-operative stays were

shorter (6.2 versus 9.9, $p = <0.001$); and overall hospital cost was less ($6871 versus $7948, $p = 0.02$) (Liang et al., 2016). This study provided no data on socio-economic status, and because the study took place at a single Chinese hospital, generalizability of the results over different races and socio-economic statuses is not possible. The significant results of this study demonstrated support of the use of ERAS protocols in laparoscopic hepatectomies (Liang et al., 2016).

Moya et al. (2016) recognized a gap in knowledge regarding ERAS in their prospective multicenter randomized single-blind clinical trial. One element of the ERAS protocol recommends using an oral immunonutrient supplement to stimulate a better immune response in the patient, leading to fewer infections. There was little clinical support for the recommendation, so Moya et al. sought to strengthen the evidence by evaluating perioperative standard oral nutrition supplements versus immunonutrition in patients undergoing colorectal resection in an enhanced recovery pathway. Two-hundred and forty-four participants were recruited and randomized into two groups (Moya et al., 2016). Participants were asked to drink two 200ml cartons of their assigned supplement per day for seven days prior to the surgery, as well as for five days post-operatively. All participants received standardized elements of ERAS, including: iron supplementation, no colon preparation, goal-directed fluid management with esophageal doppler monitoring, avoidance of drains, no nasogastric tubes, early mobilization, opioid-free pain control, and prophylactic treatment for nausea and vomiting (Moya et al., 2016). Because this study compared two ERAS protocols with only the nutritional supplements changed, the research team was able to isolate the one element on the protocol they were interested in. Outcomes studied were complication rates, broken down into surgical

complications and infectious complications (Moya et al., 2016). The immunonutrient group had fewer overall complications- 23% compared to 35.2%, as well as fewer infectious complications- 10.7% compared to 23.8% in the traditional supplement group (Moya et al., 2016). These results support the use of nutritional supplements as part of an ERAS protocol. Overall, this study demonstrated that individual elements within an ERAS protocol are continuously being studied and updated to reflect the most evidence-based recommendations.

Empirical Evidence Refuting ERAS Protocols.

While the literature suggests that ERAS protocols are successful as a whole, there are some bodies of work that suggest some of the elements may not be as useful as others. For example, Atkinson et al. (2016) conducted a clinical trial to compare postoperative chewing gum to standard care, in order to determine the effect of chewing gum on post-operative colorectal resection patients. Researchers recruited 412 patients from five UK hospitals, who were then randomized and into the two groups: chewing gum or control. Both patient groups received the same surgical procedures as well as perioperative care. After surgery, patients in the experimental group were asked to chew gum four times a day for at least ten minutes at a time, and the control group was asked to abstain from gum-chewing (Atkinson et al., 2016). The results showed no statistical difference between groups when looking at their primary outcome, length of stay, or secondary outcomes, such as time to first bowel sound, diet advancement, and first bowel movement (Atkinson, 2016). The authors suggested this result could be due to compliance issues within the two study groups, or that gum on its own is not as effective as pairing it with other ERAS elements.

ERAS Implementation.

Discrepancies in the existent literature are not limited to supporting or refuting ERAS protocols. A study by Mawdsley, Baker, Desai, Green, & Jevons (2016) demonstrates a lack of consistency in the implementation of ERAS protocols. The investigators used a prospective region-wide service evaluation to determine what differences exist in the analgesia used in enhanced recovery pathways across the northeast of England. Ninety-one cases from 5 different hospitals were examined from pre-operative through post-operative care. All participants underwent either a total hip or knee replacement and agreed to participate in an enhanced recovery pathway. Researchers designed a proforma to assess what peri-operative ERAS interventions were used in each case (Mawdsley et al., 2016). Elements that were evaluated included: preoperative medications, the use of local anesthesia, general anesthesia, or spinal anesthesia as well as postoperative medications. Three of the five facilities used a complete enhanced recovery (ER) pathway, while the other two simply included a few elements of ERAS. For preoperative analgesia, 46% of patients received nothing, 46% received gabapentin, 19% received dexamethasone, 18% received lansoprazole, and 8% received oxycontin (Mawdsley et al., 2016). In the facilities that used an ER pathway, local anesthesia was used in 96% of the cases, 4% used general anesthesia, and 96% used spinal anesthesia. For the facilities that did not use a full ER pathway, only 5% of patients received pre-operative analgesia, 38% received local anesthesia, 20% received general anesthesia, and 78% received spinal anesthesia (Mawdsley et al., 2016). Postoperatively, only oral analgesia was given the ER pathway cases, while PCA analgesia was used in 40% of the non-ER pathway surgeries. Each patient studied had a different analgesia

regimen perioperatively (Mawdsley et al., 2016). This wide variety of analgesia types and uses within an ERAS protocol points to the need to standardize analgesia and anesthesia plans for optimal implementation and effectiveness. This study was somewhat limited in its scope, as it had a small sample, and all were from one geographic location, however, it demonstrates the need for further standardization within the ERAS protocols.

These studies demonstrate the available research about enhanced recovery programs as well as the usefulness and importance of integrating these pathways into hospitals and surgery centers. In particular, studies like Abdikarim et al. (2015) and Liang et al. (2016) support the use and effectiveness of ERAS protocols for hepatectomies and gastrectomies, both general surgeries. Within the ERAS protocols, some elements are hardly studied at all, warranting more thorough research in the area, like Moya et al. (2016) demonstrated. Other elements have no real evidence to support their use. Atkinson et al. (2016) showed chewing gum to have no effect on post-operative outcomes, despite previous studies supporting its use. Finally, Mawdsley et al. (2016) points out discrepancies in the implementation of ERAS, concluding there is no standardization in the execution of ERAS protocols. Overall, this literature displays a need for a more thorough review of techniques involved in ERAS programs to determine the most effective methods.

In summary, the stress response, or more specifically, the surgical stress response, significantly alters a patient's metabolism, hormone secretion, and nervous system activation. The stress response evolved as a way for humans to have enough energy to react to stressful situations, as a survival mechanism. During surgery, that response is not necessary, and often can be detrimental to a patient's wellbeing and recovery

(Desborough, 2000). A large component to the practice of anesthesia involves attenuating the surgical stress response to keep the patient hemodynamically and otherwise stable, so surgery can be performed and only minimally interrupt the patient's homeostasis. With the research and development that has gone into enhanced recovery programs, providers have an additional mechanism to combat the stress response and improve patient outcomes and decrease recovery time, leading to shorter hospital stays. The purpose of this major paper, therefore, is to complete a systematic review of literature, in order to answer the clinical question, "which perioperative ERAS techniques are most effective in decreasing recovery time and length of stay for adults, aged 18-65, undergoing cholecystectomy surgery?"

Next, the methods used for this systematic review will be discussed.

Methods

Purpose

The purpose of this major paper was to complete a systematic review of relevant literature, in order to answer the clinical question, "which perioperative ERAS techniques are most effective in decreasing recovery time and length of stay for adults, aged 18-65, undergoing cholecystectomy surgery?"

Design & Procedure

A systematic review of current empirical literature was the research design chosen to answer the above clinical question. This review followed the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) checklist, as seen in Appendix B. PRISMA is a guideline that originated in 1987, when it was discovered that there was a wide range in quality and quantity of items being reported in research reviews. In order to be able to justify further research or clinical recommendations, standardizations in reporting were necessary. Using the PRISMA guidelines, current literature was systematically searched to select randomized controlled trials in a consistent, repeatable way. Data from the studies selected was collected, analyzed, evaluated, and reported in the same manner (Moher, Liberati, Tetzlaff, & Altman, 2009). The following sections describe these steps in further detail.

Literature Search and Selection.

For this review, the following search terms were used: "ERAS," "enhanced recovery," "fast-track surgery," "fast-track rehabilitation," and "cholecystectomy." These terms were entered into the Cochrane database, the Cumulative Index of Nursing and

Allied Health Literature (CINAHL), CINAHL Plus with Full Text, PubMed, PubMed Health, and MEDLINE.

Inclusion Criteria.

Inclusion criteria limited results to:

a) randomized controlled trials,

b) elective laparoscopic cholecystectomies

c) ASA status I-II

d) articles written in English, and

e) articles from 2014-present.

Exclusion Criteria.

Studies were excluded if they:

a) did not pertain only to adults, 18-65, or

b) involved the treatment of cancer.

The American Board of Surgery (2017) defines cholecystectomy surgery as a procedure to remove the gallbladder. The surgery can be performed open, or under laparoscopy, with video assistance. In the following section, methods for data collection, evaluation and analysis will be discussed.

Data Collection and Evaluation.

Upon selection of studies to be included, data was extracted for critical appraisal in data tables (see Appendices C and D). Information extracted from each study included the study's purpose, design, population, methods, outcomes studied, and results. The studies were evaluated for quality and strength of their evidence and was a factor when comparing data and drawing conclusions. The Critical Appraisal Skills Program (CASP)

was utilized in doing so (see Appendix E). CASP checklists were designed based on the type of research being conducted, by a group of experts over decades, in order to aid researchers in consistently evaluating validity, results, and clinical relevance (Critical Appraisal Skills Programme, 2018).

Data Analysis.

Following along the PRISMA checklist, narrative form, as well as cross-analysis charts, were used to analyze and synthesize data. The cross-study analysis compared outcomes and results across studies, and can be found in Appendix F. Primary outcomes compared in this review include recovery time and length of stay. Secondary outcomes that may have affected the primary outcomes were also compared and include, but are not limited to, extubation time, pain scores, complication rates, and medication consumption. Conclusions are drawn and discussed in an integrative summation of the data.

Results

After completing the literature search, 27 articles were screened, using inclusion and exclusion criteria. Five articles remained. Upon further assessment, one article had not published final results, and was therefore excluded. The remaining four articles will each be discussed individually in the following pages, while summaries of their content can be found in appendices C through F. A visual representation of the selection process can be seen below in Figure B-1 of Appendix B.

The first study, a prospective randomized controlled trial performed by Çaparlar et al. (2017) compared anesthesia maintained with Sevoflurane, an anesthetic gas, to total intravenous anesthesia (TIVA), using Propofol and Remifentanil infusions for patients undergoing laparoscopic cholecystectomies. Eighty participants were computer-randomized into two groups, the Sevoflurane group and the TIVA group. All participants received the same pre-operative, intra-operative, and post-operative care, as seen in the methods section of Table C-1, of Appendix C. The outcomes examined include extubation time, time from discontinuation of anesthesia to discharge, time to fast-track eligibility, discharge time, and complication rates, all of which can affect the primary outcomes examined in this review. Results are summarized in Table D-1 (see Appendix D). Researchers found a statistically significant difference in extubation time, time to fast-track eligibility, number of fast-tracked patients, and discharge times between groups (Çaparlar et al., 2017). Extubation time took an average of eight minutes for the Sevoflurane group and an average of seven minutes for the TIVA group ($p = .034$). Fast-track eligibility was reached in an average of 11.5 minutes for the Sevoflurane group and 8.5 minutes, average, in the TIVA group ($p = .010$). There were 23 patients in the Sevoflurane group and 32 in the TIVA group that were eligible for fast-track discharge (p

= .032). Discharge times for fast-tracked patients averaged 13 minutes for the Sevoflurane group and 10 minutes for the TIVA group ($p = 0.032$) (Çaparlar et al., 2017).

Utilizing the CASP tool, this article was appraised for validity, sound research, and clinical relevancy (see Table E-1, in Appendix E). Specific methods were followed so that all patients were treated as similarly as possible, apart from the treatment itself. Patients were blinded to treatment, but due to the nature of anesthesia gas versus intravenous infusions, providers were not blinded to the treatment, which could be a possible source of bias. After participants were randomized into their two groups, demographic data such as gender, age, weight, and ASA physical status were compared and found to have no statistical difference, minimizing population bias. To detect significance with an 80% power, 36 patients per group were required. Using 40 patients per study group, a 95% confidence interval was established when finding significant difference in the outcomes studied between groups. Limitations included the lack of blinding to health-workers and study-personnel, as well as not measuring a true effect size for comparison. Additionally, this study could have considered temperature maintenance as a variable to assess. Many ERAS protocols currently published include a component on patient warming, as it can affect discharge times (Fearon et al., 2005). In spite of these few limitations, this study was valid, minimized bias, and resulted in evidence that is clinically relevant.

Fanelli et al. (2014) conducted a prospective, randomized, double-blind placebo-controlled trial to evaluate whether oral morphine administered pre-operatively would improve pain control after laparoscopic cholecystectomies, ultimately leading to faster discharge times. Forty-one participants were randomized into two groups, group

oramorph and group placebo. All participants received the same pre-operative, intra-operative, and post-operative care, as seen in the methods section of Table C-2, of Appendix C. The outcomes examined that pertain to the outcomes of this review include time to first breathing, eye-opening, extubation, and awakening, as well as tramadol consumption, pain scores, postoperative nausea and/or vomiting (PONV), and anxiety. Results are summarized in Table D-2, found in Appendix D. No statistical significance was found between groups on any parameter other than pain scores with movement, during the first three hours. On this outcome, patients who had received oral morphine reported a pain score on average of 3.23/10, compared to an average pain score of 4.13/10 in patients who had received the placebo (p =.016) (Fanelli et al., 2014).

The CASP tool was used to appraise this study (see Table E-2 of Appendix E). Of the 41 patients who began this trial, 36 completed it. Dropouts were accounted for, but not well explained, leading to a potential source of bias. The two groups were well matched on baseline characteristics, however, and were treated equally throughout the perioperative period. While some efforts were taken to minimize bias, others were overlooked. The minimum number of participants required to have an 80% power of detecting significance was 18 per treatment group. This is a significant limitation of the study, as one group had 19 patients in the end, while the other had only 17. The treatment effect was not calculated for comparison, but knowing at least 18 patients per group was required, this study should have recruited a larger number of participants to compensate for dropouts, in order to have enough power to find significance. Overall, this study was well conducted and would have relevant results, apart from the lack of power to find significance.

In a double blind, randomized, controlled trial by Moro et al. (2017), investigators administered Ketamine to evaluate its effect on recovery times for patients undergoing laparoscopic cholecystectomies. One hundred thirty-five patients were computer-randomized into three groups to compare two concentrations of ketamine against saline. All participants received the same pre-operative, intra-operative, and post-operative care, as seen in the methods section of Table C-3, of Appendix C. Outcomes studied include quality of recovery (QoR-40) scores, time to eye-opening, pain scores, PONV, and post-anesthesia care unit (PACU) time. Results are summarized in Table D-3 (see Appendix D), however, no significant difference was found between groups on any parameter (Moro et al., 2017).

Using the CASP tool to appraise this study (see Table E-3 in Appendix E), it was found that this study addressed a clearly focused issue. Additionally, researchers minimized study biases by randomizing assignment and blinding all participants and providers. There were no differences found between groups on baseline characteristics, and all patients that entered this study were accounted for at its end. In spite of using more than the required 30 participants per group to have a 90% power of finding significance, no significance was found. A limitation of this study would be that they did not consider the effects of timing on the administration of Ketamine. They administered the drug at one set time point, and it was found to be ineffective, both in reducing post-operative pain and in reducing the amount of morphine consumed. Considering the study methods appear valid, the results are still relevant in that they found no significant difference between any of the groups on the outcomes studied.

Finally, Mousa, Mowafi, Al-Metwalli, Al-Ghamdi, and Al-Gameel (2015), conducted a double-blind, randomized controlled study to determine if mannitol infusions before the induction of anesthesia would enhance recovery after surgery in patients undergoing laparoscopic cholecystectomies. Forty patients were computer-randomized into two groups, group mannitol and group control. All participants received the same pre-operative, intra-operative, and post-operative care (see Appendix C, Table C-4). The outcomes examined include cerebral oxygen saturation, time to extubation, alertness/sedation scale scores, and mini-mental state examination (MMSE) scores. Results are summarized in Table D-4 of Appendix D. A significant difference was found between groups on cerebral oxygen saturation, time to extubation, and the alertness/sedation scale scores. On these parameters, the mannitol group was found to have a higher oxygen saturation 30 minutes after extubation, with a mean of 65, compared to 53 ($p < .05$). The mannitol group had a shorter extubation time, averaging 6.5 minutes compared to 9 ($p < .001$). Higher alertness/sedation scale scores at 10 minutes post-extubation were found in the mannitol group, with a median score of 4, compared to 2 ($p = .007$). There was no difference found in MMSE scores (Mousa et al., 2015).

Again utilizing the CASP tool, this article was appraised for validity and relevancy (see Appendix E, Table E-4). This trial addressed a clear issue and minimized bias by randomizing participants into groups and blinding both participants and providers to the assignment of groups. In order to have 90% power in detecting significance, 16 patients per group were required. This study recruited enough participants to have 20 in each group, so there was enough for dropouts, withdrawals, etc. There was no difference

found between groups on baseline characteristics. A limitation of this study is that they did not consider pain as a factor. Cerebral oxygen consumption would be affected by how much pain a patient is experiencing, and is therefore a relevant variable to study. Additionally, the researchers could have also assessed length of stay, not just recovery time, to further assess Mannitol's effectiveness. Overall, this study offers valid results that are relevant and have minimal risks, compared to the benefits studied.

A cross-study analysis was performed, in order to compare similarities and differences across studies, and can be found in Appendix F. The outcomes compared across studies were recovery time and length of stay. For the first study, Çaparlar et al. (2017) found that the TIVA group met fast-track eligibility faster and had shorter extubation times, both contributing to faster recovery times. Additionally, the TIVA group not only had more patients qualify for fast-track discharge, but were also discharged faster that the Sevoflurane group, effectively decreasing length of stay. In the second study, Fanelli et al. (2014) found that the morphine group reported lower pain scores in the first three hours postoperatively, which would contribute to a faster recovery time. No other differences were found between groups, so length of stay would also be similar between groups. The third study by Moro et al. (2017) found that Ketamine given just before incision had no effect on the parameters studied, and therefore did not decrease recovery time or length of stay. Finally, Mousa et al. (2015) found that Mannitol led to shorter extubation time as well as a decreased recovery time overall. Length of stay was not measured, but a shorter recovery time would lead to a shorter length of stay. Taken together, the cross-study analysis shows that oral morphine may decrease pain immediately after surgery, but has no effect on length of stay, while Ketamine has no

effect on either outcome. However, it was shown that using either Mannitol or a TIVA will not only shorten recovery time, but also lead to decreased lengths of stay.

Summary and Conclusions

The surgical stress response can have a major impact on the body, leading to prolonged recovery periods and increased hospital lengths of stay. Mitigating that response by implementing evidence-based practices, not only helps the patient recover faster, but also allows for prompter hospital discharges. Consequentially, the financial burden on both the patient and the healthcare system is lessened. Laparoscopic cholecystectomies are a noteworthy procedure to focus inquiry on regarding enhanced recovery implementations, as they are a common same-day surgery, with little variation.

This review was conducted in order to answer the question, which perioperative ERAS techniques are most effective in decreasing recovery time and length of stay for adults, aged 18-65, undergoing cholecystectomy surgery? Following PRISMA guidelines to conduct a systematic search and review, four randomized controlled trials were selected for inclusion. Upon data extraction and evaluation, results were compared across studies to evaluate the above research question and draw conclusions.

The cross-study analysis found that TIVA and mannitol can both decrease recovery time and length of stay, while oral morphine and ketamine were both found to have no effect on either outcome. Previous research comparing TIVA to gas anesthesia had conflicting results. For example, studies done by Robinson, Uhrich, and Ebert (1999) and Gupta et al. (2004) both compared TIVA to gas anesthesia and found the patients receiving gas woke faster. Conflictingly, studies by Juckenhöfel, Feisel, Shcmitt, and Biedler (1999) as well as Larsen, Seitz, and Larsen (2000) also compared TIVA to gas anesthesia and found that patients receiving TIVA woke faster. In this current systematic review, it was noted that the study by Çaparlar et al. (2016) demonstrated faster recovery

times with TIVA. However, the authors emphasized that these results were specific to a combination of propofol and a fast-acting opioid, such as remifentanil.

Enhanced recovery after surgery encompasses the use of treatments to increase oxygen flow to cerebral tissue, which is imperative in improving recovery from surgery. Mousa et al. (2015) confirmed previous findings that the induction of general anesthesia increases cerebral oxygen saturation, while insufflating the abdomen for laparoscopy decreases it. In their study, Mousa et al. also found that low-dose mannitol can effectively mitigate the decrease in cerebral oxygenation associated with insufflation when given preoperatively. Patients that received mannitol maintained their cerebral oxygen saturation, even during insufflation, leading to shorter extubation times and faster recovery.

Post-operative pain control is also key to improved recovery and decreased lengths of stay. Interestingly, the results of this review found that neither morphine nor ketamine improved recovery or decreased the length of stay. Fanelli et al. (2014) demonstrated no statistical difference between the use of morphine compared to placebo on recovery time or length of stay. A few non-significant, yet clinically notable differences were observed, however. Patients in the placebo group had higher pain scores post-operatively, a higher rate of tramadol consumption, and an increased number of patients required further supplemental medications. One possible rationale for why this study did not have significant results could be that they under-estimated their power calculation. Another is that a multi-modal pain regimen was included as part of the protocol, which could have masked the true extent to which morphine decreased pain (Fanelli et al., 2014). Moro et al. (2017) attempted to refute previous studies and show

that ketamine was effective at reducing postoperative pain. They found, however, that when used as part of a multimodal pain regimen, ketamine did not reduce post-operative pain scores. Lack of significant findings in this study could be due to multiple factors. One possible factor is that the effects of ketamine are relatively short-lived, so perhaps an infusion would be more effective. Alternatively, a larger dose may be required to see the desired effects. Similar to the Fanelli et al. study, ketamine was administered as part of a multimodal regimen, which may have masked some of the effects of ketamine (Moro et al., 2017).

In conclusion, the findings of this systematic review determined that utilizing TIVA (with propofol and remifentanil) and/or including a 20% mannitol infusion pre-induction are two ERAS techniques that may lead to improved recovery times and shorter lengths of stay for patients undergoing laparoscopic cholecystectomy surgeries. Additionally, it was found that although morphine and ketamine may be effective in reducing pain in general, their results were not found to be significant in the studies reviewed in this project.

Box 2. Study Recommendations

To improve recovery time and decrease length of stay, the following are recommendations to consider for the patient undergoing a laparoscopic cholecystectomy:

- **Total IV anesthesia (Remifentanil and Propofol infusions)**
- **Pre-induction 20% mannitol infusion**

These recommendations are in addition to other evidence-based ERAS techniques and protocols

Limitations

In order to develop ERAS protocols that are effective at decreasing the costs associated with prolonged hospital stays after surgery, all components of a patient's perioperative care should be assessed, not just their surgical care. A limitation of this research is that researchers did not assess the other components of their ERAS protocols or otherwise speak to their validity or reliability in order to ensure effectiveness. Another limitation is that only four randomized controlled trials met inclusion and exclusion criteria at the time of this review. Repeating this search in a few years will likely yield more results that will result in a more robust review. Finally, the results were limited to laparoscopic cholecystectomies, as these procedures are less invasive and offer faster recovery times than an open procedure, but expanding the search to include cholecystectomy surgeries in general would results in a more robust review, while still being specific enough to have meaning and relevance in current literature.

Recommendations and Implications for Advanced Nursing Practice

There are many health care providers involved in a patient's care from the moment they step into the hospital, until they are wheeled out at discharge. Enhanced recovery protocols involve many of these providers, in order to provide the most efficient patient-focused care. Anesthesia providers have a unique role in implementing ERAS protocols, as some of the most efficacious ways to mitigate the stress response occur at the point the stress occurs, during surgery itself. Nurse anesthetists are especially critical, as they are constantly with a patient, from the moment they leave the pre-operative area, until they safely arrive in recovery.

The Neuman Systems Model is a useful tool that can guide the advanced nurse practitioner in the application of this study's data. This model is useful in determining best practices, because it encourages the provider to look at the patient holistically to determine which environmental stressors will be a factor and how to best mitigate them. Upon identifying such stressors, the advanced practitioner can then better identify the appropriate interventions to strengthen the patient's lines of defense and resistance, therefore reducing the patient's specific stress-related response. In other words, these study recommendations should not be applied blindly to every patient. Accurate assessment, knowledge, and the use of critical judgment will guide the advanced practice nurse to implement these recommendations appropriately. Providers using these interventions should know the dosage, mechanism of action, side effect profiles, and contraindications for any medications used, and should be knowledgeable about the stress response itself and how each intervention within a given protocol further builds up a patient's line of defense.

The implications of these results extend beyond the providers implementing them. By implementing research-based ERAS protocols and their various components, nurse anesthetists are providing safer care and advancing the field of anesthesia as well as strengthening the professionalism of advanced practice nurses. Advanced practice nurses are also leaders in their field, and as such, should not only utilize and judiciously implement research-based guidelines, but should also share findings with peers. It is through this collective sharing of knowledge that the field of health care can advance and allow new and better ways of caring to emerge.

Evidence-based research is constantly evolving. There is always room for more research to improve methods for providing patient care. To continue research in this area, other investigators may look at the many other components of ERAS when developing a protocol for this particular surgical population. The techniques investigated in the laparoscopic studies reviewed in this study may also be generalized to surgeries other than laparoscopic cholecystectomies. Additionally, investigations into other surgical populations with adjusted protocols, such as pediatric or geriatric populations would be beneficial. As surgeries continue to evolve and advance, so will the peri-operative care the surgical team provides.

References

Abdikarim, I., Cao, X., Li, S., Zhao, Y., Taupyk, Y., & Wang, Q. (2015). Enhanced recovery after surgery with laparoscopic radical gastrectomy for stomach carcinomas. *World Journal of Gastroenterology, 21*(47), 13339-13344. doi:10.3748/wjg.v21.i47.13339

Atkinson, C., Penfold, C. M., Ness, A. R., Longman, R. J., Thomas, S. J., Hollingworth, W., . . . Lewis, S. J. (2016). Randomized clinical trial of postoperative chewing gum versus standard care after colorectal resection. *British Journal of Surgery, 103*(8), 962-970. doi:10.1002/bjs.10194

ABMS. (n.d.). American Board of Surgery. Retrieved July 14, 2017, from http://www.abms.org/member-boards/contact-an-abms-member-board/american-board-of-surgery/

Çaparlar, C. Ö, Özhan, M. Ö, Süzer, M. A., Yazicioğlu, D., Eşkin, M. B., Şenkal, S., . . . Çekmen, N. (2017). Fast-track anesthesia in patients undergoing outpatient laparoscopic cholecystectomy: Comparison of sevoflurane with total intravenous anesthesia. *Journal of Clinical Anesthesia*, *37*, 25-30. doi:10.1016/j.jclinane.2016.10.036

Cannon, W. B. (1915). *Bodily Changes in Pain, Hunger, Fear and Rage: An account of recent researches into the function of emotional excitement.* London and New York: D. Appleton and Company.

Clarke, R. (1970). The Hyperglycaemic Response to Different Types of Surgery and Anaesthesia. *British Journal of Anaesthesia, 42*(1), 45-53. doi:10.1093/bja/42.1.45

Critical Appraisal Skills Programme. (2018). CASP Checklist: Randomized Controlled Trial. Retrieved March 22, 2019, from https://casp-uk.net/casp-tools-checklists/

Cuthbertson, D. P. (1932). Observations on the Disturbance of Metabolism Produced by Injury to the Limbs. *QJM: An International Journal of Medicine.* doi:10.1093/oxfordjournals.qjmed.a066583

Desborough, J. (2000). The stress response to trauma and surgery. *British Journal of Anaesthesia, 85*(1), 109-117. doi: 10.1093/bja/85.1.109

Egdahl, R. H. (1959). Pituitary-Adrenal Response Following Trauma to the Isolated Leg. *Surgery, 46*(1), 9-21.

Enhanced Recovery Partnership Programme. (2010, March 31). *Delivering enhanced recovery: Helping patients to get better sooner after surgery* (UK, Department of Health, National Health Service). Retrieved from http://webarchive.nationalarchives.gov.uk/20130104172027/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_119382.pdf

Fanelli, A., Ghisi, D., Pergolotti, B., Martinotti, M., Fanelli, G., & Danelli, D. (2014). Pilot double-blinded study to assess efficacy and tolerability of morphine sulphate oral solution (Oramorph®) given preoperaticely as add-on therapy within a multimodal postoperative pain approach in patients undergoing laparoscopic cholecystectomy. *Minerva Anestesiologica*, *80*(1), 66-75.

Fearon, K., Ljungqvist, O., Meyenfeldt, M. V., Revhaug, A., Dejong, C., Lassen, K., . . . Kehlet, H. (2005). Enhanced recovery after surgery: A consensus review of

clinical care for patients undergoing colonic resection. *Clinical Nutrition, 24*(3), 466-477. doi:10.1016/j.clnu.2005.02.002

Finnerty, C. C., Mabvuure, N. T., Ali, A., Kozar, R. A., & Herndon, D. N. (2013). The Surgically Induced Stress Response. *Journal of Parenteral and Enteral Nutrition, 37*(5). Doi: 10.1177/0148607113496117

Gaubatz, C., & Wehner, R. (1991). Evalutaiton of esmolol and fentanyl in controlling increases in heart rate and blood pressure during endotracheal intubation. *Journal of the American Association of Nurse Anesthetists, 59*(1)*,* 91-96.

Greenberg, N., Carr, J., & Summers, C. (2002). Causes and Consequesnces of Stress. *Integrated and Comprehensive Biology, 43,* 508-516.

Gupta, A., Stierer, T., Zuckerman, R., Sakima, N., Parker, S.D., Fleisher, L.A. (2004). Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. *Anesth Analg, 98*(3), 632-41.

Hall, J. E., & Guyton, A. C. (2016). *Guyton and Hall Textbook of Medical Physiology.* Philadelphia: Elsevier Saunders.

Hine, I., Wood, W., Mainwaring-Burton, R., Butler, M., Irving, M., & Booker, B. (1976). The Adrenergic Response to Surgery Involving Cardiopulmonary Bypass, as Measured by Plasma and Urinary Catecholamine Concentrations. *The British Journal of Anesthesia, 48*(4)*,* 355-363.

Juckenhöfel, S., Feisel, C., Schmitt, H.J., & Biedler, A. (1999). TIVA with propofol-remifentanil or balanced anesthesia with sevoflurane-fentanyl in laparoscopic

operations: Hemodynamics, awakening and adverse effects. *Anaesthesist, 48*(11), 807-12.

Jurczok, A., Zacharias, M., Wagner, S., Hamza, A., & Paolo, F. (2007). Prospective non-randomized evaluation of four mediators of the systemic response after extraperitoneal laparoscopic and open retropubic radical prostatectomy. *BJU International, 99*(6), 1461-1466. doi: 10.1111/j.1464-410X.2007.06849.x

Larsen, B., Seitz, A., & Larsen, R. (2000). Recovery of cognitive function after remifentanil-propofol anesthesia: a comparison with desflurane and sevoflurane anesthesia. *Anesth Analg, 90*(1), 168-74.

Liang, X., Ying, H., Wang, H., Xu, H., Yu, H., Cai, L., . . . Cai, X. (2016, February). Enhanced Recovery Program Versus Traditional Care in Laparoscopic Hepatectomy. *Medicine, 95*(8), 1-6. doi:10.1097/md.0000000000002835

Martin, S. A. (1996). Applying nursing theory to the practice of nurse anesthesia. *Journal of the American Association of Nurse Anesthetists, 64*(4), 369-372.

Mawdsley, M., Baker, P., Desai, A., Green, R., & Jevons, L. (2016, May). Regional uptake and variations in orthopaedic enhanced recovery pathways in knee and hip total arthroplasty. *Journal of Perioperative Practice, 26*(5), 118-122.

McEwen, M., & Wills, E. M. (2014). *Theoretical Basis for Nursing* (4th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Moher, D., Liberati, A., Tetzlaff, J., Altman, DG, & The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA Statement. *PLoS Med 6*(7): e1000097. doi:10.1371/journal.pmed1000097

Moore, F. (1953). Bodily Changes in surgical convalescence: I- the normal sequence—observations and interpretations. *Annals of Surgery, 137*(3), 289-315.

Moro, E. T., Feitosa, I. M. P. S. S., Oliveira, R. G., Saraiva, G. F., Rosalino, R., Marossi, V. P., . . . Navarro, L. H. (2017). Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: A randomized controlled trial. *Acta Anaesthesiologica Scandinavica, 61*(7), 740-748. doi:10.1111/aas.12919

Mousa, W., Mowafi, H., Al-Metwalli, R., Al-Ghamdi, A., & Al-Gameel, H. (2015). Preoperative mannitol infusion improves perioperative cerebral oxygen saturation and enhances postoperative recovery after laparoscopic cholecystectomy. *Saudi Medical Journal, 36*(10), 1199-1204. doi:10.15537/smj.2015.10.1210

Moya, P., Soriano-Irigaray, L., Ramirez, J. M., Garcea, A., Blasco, O., Blanco, F. J., . . . Arroyo, A. (2016). Perioperative Standard Oral Nutrition Supplements Versus Immunonutrition in Patients Undergoing Colorectal Resection in an Enhanced Recovery (ERAS) Protocol. *Medicine, 95*(21), 1-11. doi:10.1097/md.0000000000003704

Neuman, B., & Fawcett, J. (2002). *The Neuman Systems Model* (4th ed.). Upper Saddle River, NJ: Prentice Hall.

NHE Fact Sheet. (2017, June 14). Retrieved July 11, 2017, from https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html

Perez, K. K., Olsen, R. J., Musick, W. L., Cernoch, P. L., Davis, J. R., Land, G. A., . . . Musser, J. M. (2013). Integrating Rapid Pathogen Identification and Antimicrobial Stewardship Significantly Decreases Hospital Costs

[Abstract]. *Archives of Pathology & Laboratory Medicine, 137*(9), 1247-1254. doi:10.5858/arpa.2012-0651-oa

Pickar, D., Cohen, M., & Dubois, M. (1983). The relationship of plasma cortisol and ß-endorphin immunoreactivity to surgical stress and postoperative analgesic requirement. *General Hospital Psychiatry, 5*(2), 93-98. doi:10.1016/0163-8343(83)90106-8

Polit, D. F., & Beck, C. T. (2017). *Nursing Research: Generating and Assessing Evidence for Nursing Practice* (10th ed.). Philadelphia: Wolters Kluwer.

Robinson, B.J., Uhrich, T.D., & Ebert, T.J. (1999). A review of recovery from sevoflurane anaesthesia: comparisons with isoflurane and propofol including meta-analysis. *Acta Anaesthesiol Scand, 43*(2), 185-90.

Sahni, N., Chigurupati, A., Kocher, B., & Cutler, D. M. (2017, May 08). How the U.S. Can Reduce Waste in Health Care Spending by $1 Trillion. Retrieved July 11, 2017, from https://hbr.org/2015/10/how-the-u-s-can-reduce-waste-in-health-care-spending-by-1-trillion

Schneiderman, N., Ironson, G., & Seigel, S. D. (2005). Stress and Health: Psychological, Behavioral, and Biological Determinents. *Annual Review of Clinical Psychology, 1*(1), 607-628. doi:10.1146/annurev.clinpsy.1.102803.144141

Selye, H. (1956). *The Stress of Life*. New York: McGraw-Hill Book.

Tsigos, C., Kyrou, I., Kassi, E., & Chrousos, G. (2016). Stress, Endocrine Physiology and Pathophysiology. In *www.endotext.org*. Retrieved July 18, 2018, from http://endotext.org/chapter/tress-endocrine-physiology-and-pathophysiology/

Ume-Nwagbo, P. N., Dewan, S. A., & Lowry, L. W. (2006). Using the Neuman Systems Model for Best Practices. *Nursing Science Quarterly, 19*(1), 31-35. doi:10.1177/0894318405284125

Appendix A- Betty Neuman Systems Model

Table A-1. Major concepts in the Neuman Systems Model

Concept	Definition
Basic Structure	"The basic structure or central core consists of common client survival factors related to system variables as well as unique individual characteristics. It represents the basic system energy resources."
Boundary Lines	"The flexible line of defense is the outer boundary of the client system. All relevant variables must be taken into account, as the whole is greater than the sum of the parts; a change in one part affects all other system parts."
Client/client system	"A total system in interaction with the internal and external environment. A composite of variables (physiological, psychological, sociocultural, developmental, and spiritual), each of which is a subpart of all parts, forms the whole of the client. The client as a system is composed of a core or basic structure of survival factors and surrounding protective concentric rings. The concentric rings are composed of similar factors, yet serve varied and different purposes in retention, attainment, or maintenance of system stability and integrity or a combination of these. The client is considered an open system in total interface and exchange of matter and information with the environment. The client is viewed as a system, and the term can be used interchangeably with the client/client system; that is, individual, family, community, and social issues are considered a system with boundaries and identifiable interacting parts."
Content	"The five variables of person in interaction with the internal and external environment comprise the whole client system."
Degree of reaction	"The degree of reaction is the degree of system instability resulting from stressor invasion of the normal line of defense."
Environment	"The environment consists of both internal and external forces surrounding the client, influencing and being influenced by the client, at any point in time, as an open system. The created environment is an unconsciously developed protective environment that binds system energy and encompasses both the internal and external client environments; it acts as a perceptual safety mechanism to maintain system stability."

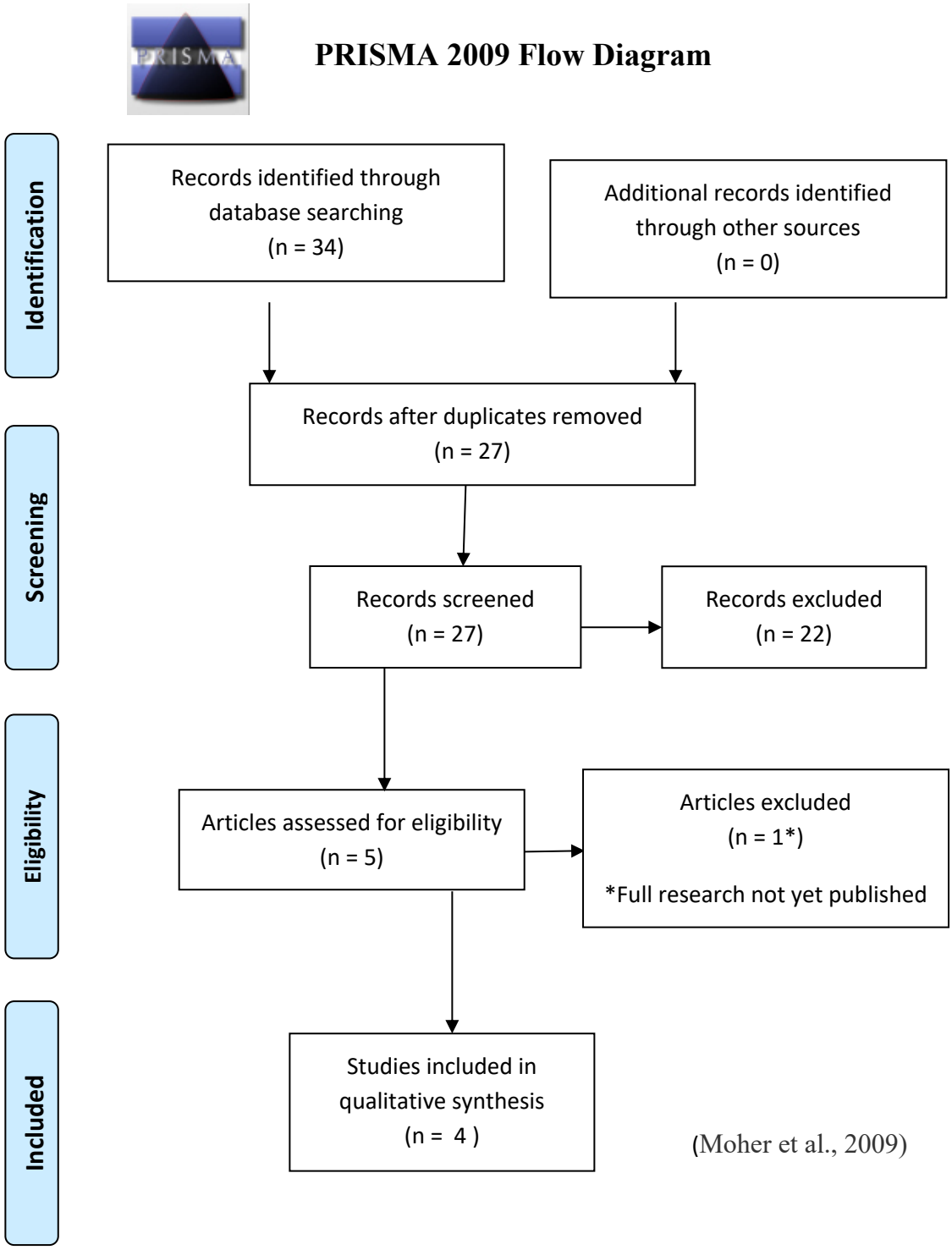
Feedback	"The process within which matter, energy, and information, as a system output, provide feedback for corrective action to change, enhance, or stabilize the system."
Flexible line of defense	"The flexible line of defense is a protective, accordionlike mechanism that surrounds and protects the normal line of defense from invasion by stressors. The greater the expansiveness of this line from the normal line of defense, the greater the degree of protectiveness. Examples are situational, such as recently altered sleep patterns or immune functions that could threaten system stability and lessen the potential for survival and optimal wellness."
Health	"A continuum of wellness to illness, dynamic in nature, that is constantly subject to change. Optimal wellness or stability indicated that total system needs are being met. A reduced state of wellness is the result of unmet systemic needs. The client is in a dynamic state of either wellness or illness, in varying degrees, at any given point in time. Health is related to available energy to support the system."
Input/output	"The matter, energy, and information exchanged between client and environment that is entering or leaving the system at any point."
Lines of resistance	"Protection factors activated when stressors have penetrated the normal line of defense, causing the reaction symptomatology. The resistance lines ideally protect the basic structure and facilitate reconstitution toward wellness during and following treatment, as the stressor reaction is decreased and client resistance is increased. All lines of defense and resistance are considered to contain both internal and external resources."
Negentropy	"A process of energy conservation that increases organization and complexity, moving the system toward stability or a higher degree of wellness. Stability and degree of wellness have a direct relationship."
Normal line of defense	"An adaptation level of health developed over time and considered normal for a particular client or system; it becomes a standard for wellness deviance determination."
Nursing	"A unique profession concerned with all variables affecting clients in their environment. Nursing is preventative intervention."
Open system	"A system in which there is a continuous flow of input and process, output and feedback. It is a system or organized complexity, where all elements are in interaction. Stress and reaction to stress are basic components."

Prevention as intervention	"Intervention typology or modes for nursing action and determinants for entry of both client and caregiver into the health care system. *Primary prevention*: before a reaction to stressors occurs. *Secondary prevention*: Treatment of symptoms following a reaction to stressors. *Tertiary prevention:* maintenance of optimal wellness following treatment."
Process/ function	"The function or process of the system is the exchange of matter, energy, and information with the environment and the interaction of the parts and subparts of the client system. A living system tents to move toward wholeness, stability, wellness, and negentropy based on effective use of available energy sources."
Reconstitution	"Represents the return and maintenance of system stability, following treatment of a stressor reaction, which may result in a higher or lower level of wellness than previously. It represents successful mobilization of energy resources."
Stability	"A desired state of balance or harmony while system energy exchanges take place without disrupting the character of the system. The dynamic nature of stability is seen as the client, as a system, adequately copes with stressors to retain, attain, or maintain optimal health and integrity."
Stressors	"Environmental factors that are intra, inter, and extrapersonal in nature and have the potential for disrupting system stability by penetrating the system lines of defense and resistance. Their outcome may be either positive or negative; client perception and coping ability are major considerations for caregivers and clients."
Wellness/illness	"Wellness is a stable condition in which system subparts are in harmony with the whole system. Wholeness is based on the interrelationships of variables, which determine the amount of resistance to stressors. Illness is on the opposite continuum from wellness and represents instability and energy depletion among the system parts or subparts affecting the whole."
Wholistic	"A system is considered wholistic when its parts or subparts can be organized into an interrelating whole. The ideal is one of keeping parts stable within their intimate relationships with the whole system; that is, individuals are viewed as wholes whose component parts are in dynamic interdependent interaction while adjusting to environmental stressors."

(Neuman & Fawcett, 2002, pg. 322-324)

Appendix B- PRISMA: Further Information

Figure B-1.



(Moher et al., 2009)

Table B-1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

(Moher et al., 2009)

Appendix C- Descriptive Data Tables

Table C-1.

TITLE	Fast-track anesthesia in patients undergoing outpatient laparoscopic cholecystectomy: Comparison of sevoflurane with total intravenous anesthesia
PURPOSE	"To compare sevoflurane anesthesia and remifentanil-propofol-based TIVA with regard to fast-track eligibility in patients undergoing outpatient laparoscopic cholecystectomy." (p. 26)
DESIGN	Prospective, randomized controlled trial
SAMPLE	- Inclusion criteria: Adult, ASA* status I-III, undergoing outpatient laparoscopic cholecystectomy, through the department of Anesthesiology at either Yildirim Beyazit Training and Research Hospital or 29 Mayis Hospital - Exclusion criteria: >40% above normal body weight, pregnant, history of intra-abdominal surgery, history of smoking or drug abuse, communication problems - Resulted with 80 Individuals, aged 31-79 years old, randomly assigned into one of two study groups: group sevoflurane or group TIVA**
METHODS	All participants: 6-hour fast pre-op; anesthesia induced with 2 mg/kg Propofol, 2 µg/kg Fentanyl, and 0.6 mg/kg Rocuronium; endotracheal tube placed 3 minutes after induction; 50% air mix used for maintenance; 10mg metoclopramide, 30 mg ketorolac, and 0.5 mg/kg meperidine were given; a total of 20ml local anesthetic mixture (containing 100mg lidocaine and 75mg bupivacaine) injected between trocar sites; reversal of paralysis with 50 µg/kg neostigmine and 20 µg/kg atropine; extubation upon spontaneous breathing and consciousness; - Group Sevoflurane: Anesthesia maintained with sevoflurane, titrated between 2-2.5% to maintain heart rate and MAP*** within 20% of baseline levels - Group TIVA: Anesthesia maintained with remifentanil-propofol drip, titrated (remifentanil: 0.1-0.2 µg/kg/min; propofol: 80-95 µg/kg/min) to maintain heart rate and MAP*** within 20% of baseline levels with 50% air
Çaparlar, C. Ö, Özhan, M. Ö, Süzer, M. A., Yazicioğlu, D., Eşkin, M. B., Şenkal, S., . . . Çekmen, N. (2017). Fast-track anesthesia in patients undergoing outpatient laparoscopic cholecystectomy: Comparison of sevoflurane with total intravenous anesthesia. *Journal of Clinical Anesthesia*, *37*, 25-30. doi:10.1016/j.jclinane.2016.10.036	

*ASA: American Society of Anesthesiologists **TIVA: Total Intravenous Anesthesia ***MAP: Mean arterial pressure

Table C-2.

TITLE	Pilot double-blinded study to assess efficacy and tolerability of morphine sulphate oral solution (Oramorph®) given preoperatively as add-on therapy within a multimodal postoperative pain approach in patients undergoing laparoscopic cholecystectomy
PURPOSE	"… to evaluate if the preoperative administration of oral morphine sulphate 30 mg (Oramorph®), within a multimodal strategy for pain therapy, could improve postoperative pain control after laparoscopic cholecystectomy, reducing theuse of opioids after surgery and leading to faster PACU discharge times" (p. 67)
DESIGN	Prospective, randomized, double-blind, placebo-controlled trial
SAMPLE	- Inclusion criteria: 18-65 years old, ASA* status I-III, undergoing elective laparoscopic cholecystectomy at the Istituti Ospitalieri di Cremona, in Cremona, Italy -Exclusion criteria: frequent use of opioids, analgesics taken during 12 hours preceding surgery, serum creatinine ≥1.4 mg/dL, dysmetabolic or hepatic failure, contraindications to any study medication, history of alcoholism or drug abuse, pregnant/breastfeeding women, and a baseline MMSE** score <24 - Resulted in 41 participants, randomized into two groups
METHODS	**All participants**: IV crystalloids started and maintained for 20 minutes prior to induction of anesthesia at 7 ml/kg/h. IVF continued at 2 ml/kg/h basal rate, with changes based on patient's hemodynamics. Pre-oxygenation for 3 minutes, followed by induction of anesthesia with remifentanil 0.5 µg/kg/min until patients felt dazed. 20mg IV Lidocaine 1%, Ketamine 0.2mg/kg, and propofol 2 mg/kg were given, followed by Cisatracurium 0.15-.2 mg/kg. Ventilation was titrated to maintain 10ml/kg tidal volume, 12 breaths/min, and ETCO2*** 30-35 mmHg. Surgery proceeded after BIS**** value reached 40-60, and BP and HR within 20% of baseline. Insufflation pressures kept between 8-12 mmHg, and room temperature kept at 21°C with 40% humidity. Oral gastric tube placed 90 minutes after treatment administration. 30mg Ketorolac given at the extraction of the gallbladder. TIVA infusions were stopped after skin closure and 0.01 mg/kg Atropine and 0.02 mg/kg Neostigmine were given. Gastric tube removed prior to patient wakening. Extubation after criteria met. PONV prophylaxis based on risk assessment- low risk: 5mg tropisetron, high risk: add 4mg dexamethasone. Postoperative PCA pump for first 24 hours. **Treatment Group Only**: 30 mg Oramorph® or placebo, taken orally, 60 minutes prior to induction of anesthesia
Fanelli, A., Ghisi, D., Pergolotti, B., Martinotti, M., Fanelli, G., & Danelli, D. (2014). Pilot double-blinded study to assess efficacy and tolerability of morphine sulphate oral solution (Oramorph®) given preoperaticely as add-on therapy within a multimodal postoperative pain approach in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiologica, 80(1), 66-75.	

* ASA: American Society of Anesthesiologists **MMSE: Mini-mental state examination ***ETCO2: End Tidal CO2 ***BIS: Bispectral Index

Table C-3.

TITLE	Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: a randomized control trial
AIM/PURPOSE	"… to assess the effect of low-dose ketamine, when used as part of a multimodal analgesic regimen, on the quality of recovery of patients undergoing laparoscopic cholecystectomy under remifentanil-propofol based anesthesia" (pg. 741)
DESIGN	Randomized, controlled, double-blinded trial
SAMPLE	Inclusion criteria: Patients undergoing laparoscopic cholecystectomy at Santa Lucinda Hospital, aged 18-65, ASA I-II; Exclusion criteria: refusal, altered level of consciousness, history of drug or alcohol abuse, contraindication to ketamine or any other medication used in this study, BMI ≥ 40 - Resulted in 135 patients, randomized into 3 groups
METHODS	- All care providers, patients, and researchers were blinded to group assignments. An independent anesthesiologist drew up the appropriate doses into identical 5ml syringes. **All participants** were induced with 0.06 mg/kg IV midazolam, 30mg 1% lidocaine, 0.5 µg/kg/min remifentanil for three minutes, 2.0 mg/kg propofol and 0.6 mg/kg rocuronium. Maintenance anesthesia was achieved with 0.3 µg/kg/min and 4-6 mg/kg/hr propofol; 8mg dexamethasone and 100mg ketoprofen were given at the onset of surgery. Ephedrine and atropine were given as needed, and normal saline was used for maintenance fluids. 15 minutes prior to the end of surgery, all participants received 30mg dimenhydrinate, 1g dipyrone, and 0.1 mg/kg morphine **Study participants** received 5ml of saline, 0.2 mg/kg ketamine in saline, or 0.4 mg/kg ketamine in saline, immediately following induction
Moro, E. T., I. M. P. S. S. Feitosa, Oliveira, R. G., Saraiva, G. F., Rosalino, R., Marossi, V. P., . . . Navarro, L. H. (2017). Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: A randomized controlled trial. Acta Anaesthesiologica Scandinavica, 61(7), 740-748. doi:10.1111/aas.12919	

Table C-4.

TITLE	Preoperative mannitol infusion improves perioperative oxygen saturation and enhances postoperative recovery after laparosopic cholecystectomy
AIM/PURPOSE	"The aim of this study was to test, whether mannitol infusion before anesthetic induction for laparoscopic surgery would improve rS02 and enhance recovery." (pg. 1200)
DESIGN	Double-blind, randomized controlled study
SAMPLE	Inclusion criteria: Willing patients undergoing laparoscopic cholecystectomy at Dammam Hospital, between December 2013-June 2014, ASA* I-II, ages 25-50 years old, BMI: 22-34 kg/m^2 Exclusion criteria: significant obstructive or restrictive pulmonary disease, significant cardiac dysfunction - Resulted in 40 patients, randomized into 2 groups
METHODS	**All participants**: Standardized anesthetic regimen used, including- induction with 2 mg/kg propofol and 2 µg/kg fentanyl, followed by 0.6 mg/kg rocuronium; anesthesia maintained with sevoflurane, titrated according to BIS monitoring; Pain and hemodynamic changes were treated with standard doses of appropriate medications; Vital signs were maintained within 20% of baseline and adequate temperature was maintained; Standard reversal doses of neostigmine/glycopyrrolate were used; patients were extubated when criteria were met; **Study participants**: Group M received 0.5 mg/kg 20% mannitol infusion 10 minutes before the induction of anesthesia. Group C received the same volume in saline
Mousa, W., Mowafi, H., Al-Metwalli, R., Al-Ghamdi, A., & Al-Gameel, H. (2015). Preoperative mannitol infusion improves perioperative cerebral oxygen saturation and enhances postoperative recovery after laparoscopic cholecystectomy. Saudi Medical Journal, 36(10), 1199-1204. doi:10.15537/smj.2015.10.1210	

* ASA: American Society of Anesthesiologists **MMSE: Mini-mental state examination

Appendix C: Outcome Data Collection Tables

Table D-1.

Outcomes	Sevoflurane Group	TIVA Group	P-value*	Significance
Extubation time (min)	t(ext)= 8 (4-12)	t(ext)= 7 (4-11)	**.034**	- Extubation time was shorter for the TIVA group
Number of fast-tracked patients, n(%)	23 (57.5)	32 (82.1)	**.018**	- More patients qualified for fast-track discharge in the TIVA group
Time from discontinuation of anesthesia to discharge, minutes: mean (range)	Fast-tracked patients: 13 (7-19) Non fast-tracked patients: 26 (21-38)	Fast-tracked patients: 10 (5-14) Non fast-tracked patients: 30 (24-34)	**.032** .228	- Fast-tracked patients were discharged faster in the TIVA group - Non fast-tracked patients saw no difference in discharge time between groups
Time after extubation to fast-track eligibility* minutes: mean (range) - for fast-tracked patients ONLY	11.5 (7-16)	8.5 (5-11)	**.010**	- Patients met fast-track eligibility faster in the TIVA group
Discharge time from PACU** (min) - for non-fast track patients ONLY	14 (10-23)	15 (10-20)	.852	- No statistical difference in discharge time from PACU was found between groups
Complication rates, n(%) HI: Hemodynamic instability PONV: postoperative nausea/vomiting	- Desaturation: 5 (12.5) - HI: 4 (10) - PONV: 4 (10) - Pain: 4 (10)	- Desaturation: 3 (7.7) - HI: 2 (5.1) - PONV: 0 (0) - Pain: 2 (5.1)	.712 .675 **.016** .675	- There was no statistical significance found in complication rates between the patients that did not meet fast-track criteria, except for the measure of PONV
Çaparlar, C. Ö, Özhan, M. Ö, Süzer, M. A., Yazicioğlu, D., Eşkin, M. B., Şenkal, S., . . . Çekmen, N. (2017). Fast-track anesthesia in patients undergoing outpatient laparoscopic cholecystectomy: Comparison of sevoflurane with total intravenous anesthesia. *Journal of Clinical Anesthesia*, *37*, 25-30. doi:10.1016/j.jclinane.2016.10.036				

*p-values < .05 was considered statistically significant **PACU: Post anesthesia care unit

Table D-2.

Outcomes	Group Oramorph®	Group Placebo	P-value*	Significance
Time Parameters Reported as: average (range)	Time to (in mins) - first breathing: 4 (0-13) - eyes opening: 7 (1-18) - extubation: 8 (2-18) - awakening: 9 (2-19) Time suture-BIS>80: 3 (1-15)	Time to (in mins) - first breathing: 2 (0-7) - eyes opening: 5 (0-11) - extubation: 5 (1-11) - awakening: 6 (1-11) Time suture-BIS>80: 4 (0-14)	 0.099 0.252 0.254 0.282 0.329	- There was no significant difference between groups on any of the time parameters studied.
Tramadol Consumption Cumulative = 24-hour total: mean ± SD (range)	Required rescue dose: n(%) 13 (76.5) Cumulative dose: 185 ± 142 mg (0- 550mg)	Required rescue dose: n(%) 18 (94.7) Cumulative dose: 263 ± 199mg (100-700mg)	 0.0668 0.0563	- While a clinical difference was noticed, there was no statistically significant difference found between groups in tramadol consumption
Pain Scores Measured during first 3 hours after awakening (mean ± SD)	- Mean pain at rest: 2.57 ± 0.26 - Mean pain with movement: 3.23 ± 0.28	- Mean pain at rest: 3.11 ± 0.25 - Mean pain with movement: 4.13 ± 0.26	 0.162 **0.035**	- There was a statistically significant difference between groups in pain scores with movement, during the first three hours of awakening
PONV n(%)	≥ 1 PONV episode: 9 (52.9)	≥ 1 PONV episode: 10 (52.6)	0.985	- No statistical difference in rates of PONV between groups
Anxiety Measured anxiety state and trait	Change in state score, at 12h: -21.99 ± 5.18 Change in state score, at 24h: -29.04 ± 5.02 Change in trait score, at 12h: -8.48 ± 4.41 Change in trait score, at 24h: -6.60 ± 3.43	Change in state score, at 12h: -24.85 ± 4.90 Change in state score, at 24h: -26.86 ± 4.75 Change in trait score, at 12h: -10.18 ± 4.04 Change in trait score, at 24h: -6.60 ± 3.43	0.691 0.754 0.784 0.412	- There was no statistical difference between groups on anxiety score changes when compared to pre-medication scores, at both 12 and 24 hours

Fanelli, A., Ghisi, D., Pergolotti, B., Martinotti, M., Fanelli, G., & Danelli, D. (2014). Pilot double-blinded study to assess efficacy and tolerability of morphine sulphate oral solution (Oramorph®) given preoperaticely as add-on therapy within a multimodal postoperative pain approach in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiologica, 80(1), 66-75.

*p-values < .05 was considered statistically significant

Table D-3.

Outcomes	Group: Saline n= 39	Group: K2 n= 37 (0.2 mg/kg Ketamine)	Group: K4 n= 43 (0.4 mg/kg Ketamine)	P-values (Using ANOVA, then Tukey's multiple comparison test)	Significance
QoR-40 Score Quality of recovery questionnaire (mean ± SD)	190 ± 10.3	191 ± 7.3	187 ± 11.5	0.54	- No significant difference found between groups
Time to eye opening Minutes (mean ± SD)	15.4 ± 5.2	15.1 ± 5.1	16.0 ± 5.3	0.70	- No significant difference found between groups
Pain Score Numerical Rating Score (mean ± SD)	3.8 ± 3.6	2.6 ± 3.2	2.8 ± 3.0	0.27	- No significant difference found between groups
PONV Incidence: n(%)	12 (30.8)	11 (29.7)	17 (39.5)	0.59	- No significant difference found between groups
PACU time Minutes (mean ± SD)	82.9 ± 23.9	84.5 ±16.6	86.0 ± 34.0	0.87	- No significant difference found between groups
Moro, E. T., I. M. P. S. S. Feitosa, Oliveira, R. G., Saraiva, G. F., Rosalino, R., Marossi, V. P., . . . Navarro, L. H. (2017). Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: A randomized controlled trial. Acta Anaesthesiologica Scandinavica, 61(7), 740-748. doi:10.1111/aas.12919					

Table D-4.

Outcomes	Group M: Mannitol Infusion	Group C: Control	P-values	Significance
Cerebral Oxygen Saturation (rS02) rSO2: Mean ± 95% CI	30 minutes after extubation: 65 ± 3	30 minutes after extubation: 53 ± 3	**p < 0.05**	- Significant difference in cerebral oxygen saturation between groups at T5;
Time to extubation Minutes: average ± SD	6.5 ± 1	9 ± 2	**p < 0.001**	- Significantly shorter in the mannitol group
Observer's Assesment of Alertness/Sedation (OOAS) Scale median (interquartile range)	10 minutes after extubation: 4 (3-4) 20 minutes after extubation: no difference	10 minutes after extubation: 2 (2-4)	**p = 0.007**	- Significantly higher in the mannitol group, at ten minutes
Mini-mental State Examination (MMSE) median (interquartile range)	10 minutes after extubation: no difference	10 minutes after extubation: no difference	P > 0.05	- No difference found between groups
Mousa, W., Mowafi, H., Al-Metwalli, R., Al-Ghamdi, A., & Al-Gameel, H. (2015). Preoperative mannitol infusion improves perioperative cerebral oxygen saturation and enhances postoperative recovery after laparoscopic cholecystectomy. Saudi Medical Journal, 36(10), 1199-1204. doi:10.15537/smj.2015.10.1210				

Appendix E: Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist Tables

Table E-1.

Çaparlar, C. Ö, Özhan, M. Ö, Süzer, M. A., Yazicioğlu, D., Eşkin, M. B., Şenkal, S., . . . Çekmen, N. (2017). Fast-track anesthesia in patients undergoing outpatient laparoscopic cholecystectomy: Comparison of sevoflurane with total intravenous anesthesia. *Journal of Clinical Anesthesia*, *37*, 25-30. doi:10.1016/j.jclinane.2016.10.036				
Question	**Yes**	**Can't Tell**	**No**	**Comments**
1. Did the trial address a clearly focused issue?	X			
2. Was the assignment of patients to treatments randomized?	X			Computer-randomization
3. Were all the patients who entered the trial properly accounted for at its conclusion?	X			
4. Were patients, health workers and study personnel "blind" to treatment?			X	Due to the nature of gas versus IV anesthetics, neither participants, nor healthcare workers were blinded to group assignment
5. Were the groups similar at the start of the trial?	X			
6. Aside from the experimental intervention, were the groups treated equally?	X			See Appendix B-1: Methods
7. How large was the treatment effect?	Using 36+ patients in each group achieves an 80% power to detect the determined odds-ratio			
8. How precise was the estimate of ttreatment effect?	95% confidence was established, but true effect size was not measured for comparison			
9. Can the results be applied to the local population, or in your context?	X			The patients are similar in baseline characteristics to the patients encountered in my practice;
10. Were all clinically important outcomes considered?			X	Temperature maintenance was not considered, and could be considered clinically relevant.
11. Are the benefits worth the harms and costs?	X			There were minimal risks. Implementation would help lower costs and increase safety and efficiency

(Critical Appraisal Skills Programme, 2018)

Table E-2.

Fanelli, A., Ghisi, D., Pergolotti, B., Martinotti, M., Fanelli, G., & Danelli, D. (2014). Pilot double-blinded study to assess efficacy and tolerability of morphine sulphate oral solution (Oramorph®) given preoperaticely as add-on therapy within a multimodal postoperative pain approach in patients undergoing laparoscopic cholecystectomy. Minerva Anestesiologica, 80(1), 66-75.				
Question	**Yes**	**Can't Tell**	**No**	**Comments**
1. Did the trial address a clearly focused issue?	X			
2. Was the assignment of patients to treatments randomized?	X			
3. Were all the patients who entered the trial properly accounted for at its conclusion?	X			41 patients were screened and randomized; 36 patients were included in the final results, with the other 5 patients accounted for
4. Were patients, health workers and study personnel "blind" to treatment?	X			Patients, providers, and data collectors were blind to group assignment
5. Were the groups similar at the start of the trial?	X			When comparing groups, no significant difference was found between gender, race, age, weight, height, ASA status, and baseline MMSE and Apfel's scores
6. Aside from the experimental intervention, were the groups treated equally?	X			See Appendix B-2: Methods
7. How large was the treatment effect?	18 patients per treatment group was required to have an 80% power			
8. How precise was the estimate of the treatment effect?	"NRS Values during the first 3 hours after awakening were lower than expected in both groups, which indicated that the power calculation could be under-dimensioned" (pg. 72)			
9. Can the results be applied to the local population, or in your context?	X			The patients are similar in baseline characteristics to the patients encountered in my practice;
10. Were all clinically important outcomes considered?	X			Many relevant primary and secondary outcomes were considered
11. Are the benefits worth the harms and costs?		X		Treatment had no discernable effect and frequency of adverse events was similar between groups

(Critical Appraisal Skills Programme, 2018)

Table E-3.

Moro, E. T., I. M. P. S. S. Feitosa, Oliveira, R. G., Saraiva, G. F., Rosalino, R., Marossi, V. P., . . . Navarro, L. H. (2017). Ketamine does not enhance the quality of recovery following laparoscopic cholecystectomy: A randomized controlled trial. Acta Anaesthesiologica Scandinavica, 61(7), 740-748. doi:10.1111/aas.12919				
Question	**Yes**	**Can't Tell**	**No**	**Comments**
1. Did the trial address a clearly focused issue?	X			
2. Was the assignment of patients to treatments randomized?	X			Computer-randomized
3. Were all the patients who entered the trial properly accounted for at its conclusion?	X			135 patients were enrolled, with all exclusions and dropouts accounted for
4. Were patients, health workers and study personnel "blind" to treatment?	X			All patients, providers, and researchers were blind to the treatment groups
5. Were the groups similar at the start of the trial?	X			There was no difference found between patient characteristics
6. Aside from the experimental intervention, were the groups treated equally?	X			See Appendix B-2: Methods
7. How large was the treatment effect?	To detect a 10-point difference in QoR-40 score, with 90% power, 30 participants per group were needed			
8. How precise was the estimate of the treatment effect?	It was not precise, as no difference was found;			
9. Can the results be applied to the local population, or in your context?	X			The patients are similar in baseline characteristics to the patients encountered in my practice;
10. Were all clinically important outcomes considered?	X			
11. Are the benefits worth the harms and costs?		X		No difference was found in outcomes between groups and frequency of adverse events was similar as well

(Critical Appraisal Skills Programme, 2018)

Table E-4.

Mousa, W., Mowafi, H., Al-Metwalli, R., Al-Ghamdi, A., & Al-Gameel, H. (2015). Preoperative mannitol infusion improves perioperative cerebral oxygen saturation and enhances postoperative recovery after laparoscopic cholecystectomy. Saudi Medical Journal, 36(10), 1199-1204. doi:10.15537/smj.2015.10.12105				
Question	**Yes**	**Can't Tell**	**No**	**Comments**
1. Did the trial address a clearly focused issue?	X			
2. Was the assignment of patients to treatments randomized?	X			Computer-randomization
3. Were all the patients who entered the trial properly accounted for at its conclusion?	X			
4. Were patients, health workers and study personnel "blind" to treatment?	X			Data collectors were blinded
5. Were the groups similar at the start of the trial?	X			
6. Aside from the experimental intervention, were the groups treated equally?	X			See Appendix B-4: Methods
7. How large was the treatment effect?	To detect a 20% difference in cerebral oxygen saturation with 90% power, 16 patients per group are needed			
8. How precise was the estimate of the treatment	Significance was found, but no treatment estimate was calculated for			
9. Can the results be applied to the local population, or in your context?	X			Inclusion/Exclusion criteria matched, along with procedure and other methods
10. Were all clinically important outcomes considered?			X	Pain was not addressed. Cerebral oxygen consumption would be affected by how much pain a patient may have been in.
11. Are the benefits worth the harms and costs?	X			In my opinion; there were minimal risks to receiving the study drug, and the implications would help decrease costs, while increasing safety and efficiency

(Critical Appraisal Skills Programme, 2018)

Appendix F: Cross-Study Analysis

Table F-1.

Authors & Year	**Study Comparisons**	**Outcome #1: Recovery Time**	**Outcome #2: Length of Stay**	**Comments**
Çaparlar, C. Ö, Özhan, M. Ö, Süzer, M. A., Yazicioğlu, D., Eşkin, M. B., Şenkal, S., . . . Çekmen, N. (2017)	Sevoflurane vs. TIVA*	- Patients met fast-track eligibility faster in the TIVA group - Extubation time was shorter for the TIVA group	- More patients qualified for fast-track discharge in the TIVA group - fast-tracked patients were discharged faster from the TIVA group	- TIVA was found to produce both faster recovery times, and shorter lengths of stays
Fanelli, A., Ghisi, D., Pergolotti, B., Martinotti, M., Fanelli, G., & Danelli, D. (2014)	Morphine vs. Placebo	- The morphine group reported lower pain scores with movement in the first 3 hours postop	- Showed no difference between groups on PONV** score, tramadol consumption, anxiety, pain at rest, or on any time parameters	- Morphine may improve short-term recovery within the first 3 hours, but it had no effect on length of stay, or any other parameters measured
Moro, E. T., I. M. P. S. S. Feitosa, Oliveira, R. G., Saraiva, G. F., Rosalino, R., Marossi, V. P., . . . Navarro, L. H. (2017)	Ketamine at 0.2 mg/kg vs. Ketamine at 0.4 mg/kg vs. Saline	- No significant difference found between groups	- No significant difference found between groups	- Ketamine has no effect on recovery time or length of stay
Mousa, W., Mowafi, H., Al-Metwalli, R., Al-Ghamdi, A., & Al-Gameel, H. (2015)	Mannitol vs. Saline	- Extubation time was shorter and recovery time was faster in the mannitol group	- Not measured	- Mannitol was shown to have faster recovery times, which should in turn, lead to shorter lengths of stay

*TIVA: Total Intravenous Anesthesia **PONV: Post-operative nausea/vomiting