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# Dexamethasone in the Adult Diabetic Surgical Patient

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# THE USE OF DEXAMETHASONE IN THE ADULT DIABETIC SURGICAL POPULATION FOR THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING: A SYSTEMATIC REVIEW

by

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**Abstract**

Diabetes mellitus is one of the most common diseases, with a 200% predicted increase in prevalence over the next several decades (Kadoi, 2010). With a known increase in perioperative risk, diabetic patients present with multiple comorbidities that must be considered when adopting an anesthetic plan (Kadoi, 2010). One of the most common complications affecting approximately 50% of patients, is gastroparesis resulting from the development of diabetic autonomic neuropathy. Gastroparesis places the diabetic patient at an increased risk of aspiration and also postoperative nausea and vomiting (PONV). Dexamethasone is a glucocorticoid that is one of the most common prophylactic antiemetics used to prevent PONV. Dexamethasone has been associated with an increase in blood glucose levels which can be detrimental to the diabetic surgical patient (Shaikh et al., 2016). The purpose of this systematic review was to investigate the current literature and examine the impact of dexamethasone on blood glucose levels in the adult diabetic surgical patient when used in the prevention of PONV. A comprehensive literature review was completed using CINAHL and PubMed databases. The physiology and perioperative management of diabetes and PONV, along with the pharmacodynamics of dexamethasone was reviewed. Eligible studies were chosen based on guidance from the PRISMA theoretical framework. Study analysis was completed by constructing study specific and data outcome tables. Critical appraisal of individual RCTs was conducted utilizing the Critical Appraisal Skills Programme (CASP) checklist. A cross study analysis table was also developed comparing the results of all eligible studies against one another. The findings of this systematic review concluded

dexamethasone 8mg IV was associated with an increase in perioperative blood glucose levels, although, the increase may not have been statistically significant.

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# The Use of Dexamethasone in the Adult Diabetic Surgical Population for the Prevention of Postoperative Nausea and Vomiting: A Systematic Review

## Background/Statement of the Problem

Diabetic patients present to surgery with independent risk factors. Patients with hyperglycemia during the surgical period are at a greater risk for electrolyte imbalances, dehydration, increased risk of infection, fluid shifts, compromised wound healing, and ketoacidosis (Joshi et al., 2010). Diabetic patients often have other associated comorbidities resulting from chronic inadequate blood glucose control. Microvascular changes are often seen in the retinal and renal vessels, impacting sight and kidney function. Peripheral neuropathy and increased infection risk also need to be taken into consideration during the perioperative period. One of the most severe complications associated with diabetes is the presence of autonomic neuropathy. Diabetic autonomic neuropathy is a condition characterized by damage to small autonomic nerve fibers resulting in greater decline in blood pressure and increased need of vasopressors in the perioperative period. Other symptoms accompanying diabetic autonomic neuropathy include hypotension associated with position changes, impotence, diarrhea, sweating abnormalities and delayed gastric emptying. Diabetic patients with autonomic neuropathy are at an elevated risk for postoperative nausea and vomiting (PONV) and gastric aspiration due to gastroparesis (Miller et al., 2015).

PONV occur in 20% to 40% of all surgical patients and is the second most common complaint secondary to pain (Cao et al., 2017). The occurrence of PONV can delay recovery, prolong discharge, and result in unanticipated hospital admission. It also places the patient at a higher risk of developing pulmonary aspiration, electrolyte

imbalances, wound dehiscence, and dehydration. All of these complications result in increased distress on the patient and increased medical costs (Shaikh et al., 2016).

Despite a considerable amount of research conducted and strategies developed, there has not been a consensus on an optimal regimen to treat PONV. However, there has been emphasis in literature and practice on the anticipatory rather than reactionary treatment. Dexamethasone is a glucocorticoid steroid that is one of the most common anticipatory antiemetics used. The use of dexamethasone is associated with potential risks including impaired wound healing, increased blood glucose levels, and an increase risk of infection (Miller et al., 2015). These risk factors make its use in the diabetic population controversial. Therefore, this study examines the impact of dexamethasone on blood glucose levels in the adult diabetic surgical patient when used in the prevention of PONV.

Next, a literature review will be presented.

## Literature Review

A literature review was preformed to examine information about the use of dexamethasone in diabetic patients to prevent PONV. Databases searched were PubMed, Medline, CINAHL, and google scholar. Search words included dexamethasone, diabetes, and postoperative nausea and vomiting. Randomized control trials, evidence-based reviews, and guidelines were included in this literature review.

### Diabetes Mellitus

In 2015, 30.3 million Americans had diabetes with an additional 1.5 million new cases added each year (ADA, 2015). Diabetes was the seventh leading cause of death in 2015 (ADA, 2015) with a mortality rate three times higher than the average population (Kadoi, 2010). Although, a diagnosis of diabetes is not an independent risk factor for the development of PONV, approximately 50% of diabetic patients suffer from gastroparesis or delayed gastric emptying. This delayed emptying can result in a cascade of injurious events in which the increase in gastric volume can contribute to the development of symptoms of nausea and vomiting, but also induce aspiration of gastric contents during induction of anesthesia (Kadoi, 2010). With aspiration being the number one cause of airway-related mortality for anesthesia providers, a probable increase in gastric contents of diabetic patients prompts serious consideration and planning during the perioperative period (Robinson & Davidson, 2014).

**Pathophysiology.** Diabetes Mellitus (DM) is a group of disorders sharing the clinical feature of absolute or relative lack of insulin. DM is diagnosed with a fasting blood glucose (BG) of greater than 110 mg/dL (6.1 mmol/L) (Miller et al, 2015). Impaired glucose tolerance can be diagnosed with a fasting BG of 109 mg/dL – 100

mg/dL (6.1 mmol/L – 5.5 mmol/L) (Miller et al, 2015). DM is characterized by multiple metabolic abnormalities that can result in microvascular lesions and long-term end-organ damage. The term "diabetes" can account for two different diseases that share the same complication of end-organ damage: type 1 and type 2 (Miller et al, 2015).

Type 1 DM occurs when a patient is unable to produce insulin. Insulin is produced in the pancreas by beta cells; these cells are susceptible to viral infections and/or autoimmune disorders. Cellular metabolism is dependent on glucose metabolism which is fielded by insulin. Lack of insulin production not only results in high glucose levels but it also forces the body into generating alternative fuel. The alternative fuel source can be derived from the breakdown of fats and proteins. An increase in keto acid byproducts from the destruction of fats and proteins can result in the development of ketoacidosis and lead to diabetic coma and death (Miller et al, 2015).

Type 2 DM results when there is a decreased response to insulin at the target tissues. Type 2 diabetics account for 90 to 95% of all cases of diabetes. This disease has a gradual onset and generally develops after the age of 30. The greatest risk factor for the development of type 2 DM is obesity. The direct mechanism in which type 2 DM is acquired is uncertain, however, it has been suggested that obese patients have fewer insulin receptors. Another hypothesis suggests that due to increase lipid concentration, signaling pathways between insulin and its receptors are interrupted (Hall, 2011).

**Perioperative Blood Glucose Management.** There is a lack of clear evidence to suggest the optimal intraoperative glucose level, thus it remains unknown. The Society for Ambulatory Anesthesia (SAMBA) published a consensus statement on diabetic perioperative glucose management based on hospitalized surgical patient data and also

the joint consensus statement from the American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA) in 2010. SAMBA recommends an individualized approach for glucose control; duration of surgery, degree of surgical invasiveness, anesthetic choice, and expected time until resumption of antidiabetic therapy must be considered. For the well-controlled diabetic patient, intraoperative BG levels should be maintained <180 mg/dL (10.0 mmol/L). Poorly controlled diabetics need a more modest approach to glucose control. Patients with chronically elevated BG levels should be maintained around their preoperative baseline. Chronic hyperglycemia results in the alteration of autoregulatory mechanisms. Adaptations in the release of norepinephrine, epinephrine, cortisol, growth hormone, and pancreatic polypeptides can occur. An acute drop in BG can result in symptomatic hypoglycemia and organ dysfunction due to the body being accustomed to hyperglycemia. An increase in the oxidative stress response can also occur. Such acute fluctuations in the chronic hyperglycemic patient may increase morbidity and mortality, perioperatively (Joshi et al., 2010).

**Surgical Stress Response.** Under times of stress and surgical stimulation, the body responds to this stimulus with a wide range of endocrine, biochemical, and metabolic reactions. The degree of response is in direct proportion to the stimuli. This response is called the *surgical stress response* and although general anesthesia abolishes awareness and perception, it does not suppress the coordinated response from the autonomic nervous system and the neuro-endocrinal hormone system. These systems release a variety of catabolic and anabolic hormones triggering a hypermetabolic state. This state is generally well tolerated amongst healthy patients, however, in patient

populations with coronary artery disease, hypertension, aneurysmal disease, diabetes, liver or renal disease these hypermetabolic changes increase mortality (Singh, 2003).

One of the main reactions to the stress response is stimulation of the hypothalamus resulting in secretion of ACTH, which initiates a sudden increase of cortisol, the main endogenous glucocorticoid. Cortisol has the ability to stimulate the mobilization of amino acids to be converted into glucose, a process known as gluconeogenesis (Singh, 2003). Cortisol also decreases glucose utilization by the cell, further increasing hyperglycemia. Singh (2003) reports blood glucose levels can increase by 50% from the preoperative normal.

To further increase hyperglycemia, Desborough (2000) describes an "insulin resistant" state that also occurs during the perioperative phase. Insulin levels can decrease after induction of anesthesia due to failure of secretion by beta cells of the pancreas and also failure of cellular response to insulin (Desborough, 2000). Another contribution to the hyperglycemic response to major surgery is the transient increase in glucagon. Glucagon is a hormone produced by the alpha cells of the pancreas, which promotes glycogenolysis, the breakdown of glycogen to glucose. Glucagon also promotes gluconeogenesis, further increasing blood glucose levels (Desborough, 2000)

Regional anesthesia uses local anesthetics to produce a neural blockade which has direct influence on the metabolic and endocrinal response. The inhibition of afferent and efferent neural pathways prevents surgical stimulus from reaching the central nervous system (Singh, 2003). Singh (2003) reports that a neuraxial blockade from T4 to S4 prevents the cortisol response during lower abdominal surgeries. In order to prevent the insulin and glucagon response, a higher blockade from T2 to T6 is required, however,

this level of blockade is often contradicted due detrimental alterations in cardiac function that can occur (Singh, 2003).

Diabetic patients have been hypothesized to be in a chronic inflammatory state when compared to nondiabetic healthy patients (Lin & Gletsu-Miller, 2012). This chronic inflammatory state can be potentiated under surgical stress, leading to deleterious outcomes (Lin & Gletsu-Miller, 2012). A study done by Lin and Gletsu-Miller (2012) aimed to investigate the differences in the surgical stress response between diabetic and nondiabetic patients undergoing laparoscopic Roux-en-Y gastric bypass by measuring inflammatory cytokine levels. The study measured cytokine levels (IL-6, IL-10, and IL-18) preoperatively and immediately after surgery in 39 morbidly obese patients (nine with type 2 diabetes) and eight non-obese, normoglycemic patients (Lin & Gletsu-Miller, 2012). The results demonstrated an overall increase in in cytokine expression in the diabetic and morbidly obese patients by several folds in comparison to the non-obese, normoglycemic groups. At baseline, a higher IL-6 level was exhibited in the morbidly obese group compared to the non-obese group ($5.7 \pm 1.3$ pg/ml and $2.7 \pm 0.6$ pg/ml, respectively, $p < 0.05$). The IL-6 response was induced highest amongst the diabetic, obese group ($78.9 \pm 12.3$ pg/ml); a modest response in the non-diabetic, obese group ($61.0 \pm 5$ pg/ml); and the lowest response in the non-obese group ($36.3 \pm 7.2$ pg/ml) ($p < 0.01$). Consistent findings occurred with the IL-10 response. At baseline, the IL-10 levels were $1.5 \pm 0.4$ pg/ml, $1.2 \pm 0.3$, and $1.3 \pm 0.3$ pg/ml for non-diabetic, obese; diabetic obese; and non-obese groups, respectively. The greatest IL-10 response occurred in the obese, diabetic group ($65.8 \pm 1.9$pg/ml, $p < 0.001$). The non-diabetic, obese group and non-obese group levels were not significant but did increase post-

operatively (15.1 ± 5.0 pg/ml and 8.5 ± 2.7pg/ml). It was found that preoperative IL-18 levels were significantly increased in the diabetic, obese patients (450.6 ± 56 pg/ml, $p < 0.01$) compared to the non-diabetic, obese group (297.8 ± 19pg/ml) and non-obese group (286.6 ± 17pg/ml). However, post-operatively there was almost zero change to all three groups (diabetic obese: 457.9 ± 64 pg/ml; non-diabetic obese: 300 ± 26 pg/ml; non-obese: 271 ± 31 pg/ml) (Lin & Gletsu-Miller, 2012). These results demonstrate a clear increase in the surgical stress response in diabetic patients. An excessive or perpetual inflammatory response can overwhelm the patient's compensatory mechanisms, potentiating multi-organ failure leading to demise (Lin & Gletsu-Miller, 2012). Careful consideration must be made when choosing an anesthetic plan for a diabetic patient; the use of an additional glucocorticoid, dexamethasone, can further increase cortisol levels thus contributing to an increased surgical stress response.

**Perioperative Risks**. Perioperative risk factors vary based on individual health practices and lifestyle choices. Diabetic patients undergoing surgery are at risk for complications associated with end-organ dysfunction: renal insufficiency, cardiovascular deterioration, joint and collagen tissue irregularities, neuropathies and inadequate production of granulocytes (Grossman & Porth, 2014).

In a study done by Ghildiyal et al. (2016), perioperative hyperglycemia and the incidence of postoperative infection was examined. The researchers conducted a prospective study including 101 patients undergoing a variety of procedures. Random blood sugars were taken preoperatively, intraoperatively, and postoperatively. A 30-day postoperative follow-up was done evaluating for surgical wound infection, septicemia, and urinary tract infections. Fifty-seven out of the 101 patients did have an incidence of

hyperglycemia. The hyperglycemic patients developed infections at a rate of 26.3% (15/57) compared to normoglycemic patients at 4.5% (2/44) (Ghildiyal et al., 2016).

In a retrospective cohort study performed by Guvener et al. (2002) aimed to examine perioperative hyperglycemia and the incidence of postoperative infection in diabetic patients undergoing coronary artery bypass grafting. The researchers examined 1090 adult charts, 400 out of 1090 patients had type 2 diabetes mellitus. The researchers determined preoperative hyperglycemia to be the main risk factor for development of an infection postoperatively. Twenty (5%) out of the 400 diabetic patients developed postoperative infections which included: lung infections (0.5%), superficial sternal wound infections (0.75%), infection of the donor site (1%), mediastinitis (1.25%), and urinary tract infections (1.5%) (Guvener et al., 2002). It was also concluded diabetics had a higher incidence of early mortality compared to nondiabetics (3% vs 1.73%, $p$ = 0.048) (Guvener et al., 2002).

Likewise, a prospective study conducted by O'Sullivan et al. (2006) focused on the impact of hemoglobin A1c (HbA1c) levels on adverse outcomes in non-diabetic and diabetic patients undergoing elective and emergency vascular surgery. For six months the researchers collected HbA1c levels on 165 patients. Patients were classified into four groups determined by their plasma HbA1c levels: ≤ 6%, 6.1-7%, 7.1-8%, or > 8%. Outcomes were determined on any cause of 30-day or 6-month morbidity and mortality. Forty-three out of 165 (26.1%) patients had diabetes. The term "suboptimal" was used to describe nondiabetic patients with HbA1c levels of > 6 to ≤ 7% and diabetic patients with HbA1c levels of > 7% (O'Sullivan et al., 2006). The researchers concluded the suboptimal non-diabetic patients had significantly higher rates of general 30-day

morbidity versus patients with HbA1c levels of ≤ 6% (56.5% vs 15.7%, $p < 0.001$). Correspondingly, when compared to diabetic patients with HgbA1c levels of ≤ 7%, suboptimal diabetics with HbA1c levels of > 7% also had a higher rate of morbidity over 30 days (59.1% vs 19%, $p = 0.018$) (O'Sullivan et al., 2006). In conclusion, the investigators determined, with a multivariate analysis, a suboptimal HbA1c may infer prognostic significance in patients enduring vascular surgery (O'Sullivan et al., 2006). Due to the increased rate of morbidity related to hyperglycemia, perioperative blood sugar management becomes an essential part of anesthetic care. The use of dexamethasone has shown deleterious effects on blood sugars (Joshi et al., 2010), therefore this study evaluates its use for PONV in the diabetic patient and the effects on blood sugar levels.

**Diabetic Autonomic Neuropathy and Gastroparesis.** According to gastric emptying studies done using radio isotopic techniques, approximately 50% of insulin dependent diabetic patients acquire autonomic neuropathy that results in impaired gastric emptying (Kadoi, 2010). Neuropathy is caused by two mechanisms. The first mechanism is related to vascular thickening which causes neural ischemia and dysfunction. The second mechanism is due to Schwann cell demyelination leading to slow neural conductance. Neuropathy can be of somatic nature, which usually occurs first. The patient experiences the loss of proprioception, touch, and sensation (Grossman & Porth, 2014). Autonomic neuropathy affects both the sympathetic and parasympathetic nervous systems. Sympathetic denervation affects small arterioles; the nerves are either absent or located at a distance from the arteriole. Vagal impairment can be manifested by a decrease in cardiac response and decreased parasympathetic tone.

This decline in vagal function leads to postural hypotension, sweating abnormalities, impotence, diarrhea or gastroparesis. There is a 5-year mortality rate of greater than 50% when a patient develops gastroparesis or postural hypotension (Miller et al., 2015). Diabetic patients with autonomic neuropathy are at an elevated risk for PONV and gastric aspiration due to gastroparesis. This is of clinical significance when diabetic patients present for surgery, specifically emergency procedures in which they have not been fasting (Miller et al., 2015). A case report published by Tokumine et al. (2005) discussed a 28-year-old patient with a history of type I diabetes since age 12. The patient presented for an elective eye procedure and had been fasting for 12 hours. Upon induction of anesthesia the patient vomited and aspirated stomach contents that he had consumed 24 hours prior to surgery (Tokumine et al., 2005). The authors report that 30% of patients with type II diabetes and 58% of patients with type I diabetes have impaired gastric emptying. Consideration of delayed gastric transport having the potential to increase the incidence of PONV, coupled with an increased risk of aspiration of gastric contents is imperative knowledge when developing an anesthetic plan for diabetic patients (Tokumine et al., 2005).

**Postoperative Nausea Vomiting**

**Physiology.** Postoperative nausea and vomiting develop when an ill-defined area in the brain known as the "vomiting center" is stimulated by one or more of the five primary afferent neuronal pathways: the *chemoreceptor trigger zone (CRTZ)*, the *vagal afferents of the gastrointestinal tract*, the *vestibular system pathway*, *cerebral cortex afferent pathway*, and *afferents from the midbrain*. Stimulation of one or more of these pathways occurs via activation of muscarinic, histamine, dopamine, or serotonin

receptors (Shaikh et al., 2016). The *CRTZ* lacks the blood brain barrier, allowing for interaction and detection of emetogenic substances by the central nervous system via the bloodstream. Apomorphine and opioids act on this area via serotonin (5-hydroxytryptamine [5-HT]), dopamine ($D_2$), $M_3$- muscarinic, and histamine ($H_1$) receptors. (Miller et al., 2015). The *vagal mucosal afferent pathway* contains 5-HT, $M_3$, and $H_3$ receptors. This pathway is stimulated by nitrous oxide, opioids, cardiac glycosides, cytotoxic drugs, levodopa, bromocriptine, and ipecac (Shaikh et al., 2016). The *vestibular pathway* contains $H_1$ and muscarinic receptors, which are receptive to nitrous oxide. This area is also stimulated heavily by positional changes, ear surgery, and motion sickness. The *cerebral cortex* is fed and activated by emotions, fear, memory, smell, sight, and taste. Nausea will result once the cerebral cortex has been stimulated in such a manner. Lastly, *the midbrain* receives sensory information from the pharynx via the gag reflex, esophagus, stomach, and upper portions of the small intestines which is then conveyed to the vomiting center (Shaikh et al., 2016).

The vomiting center is located in the reticular formation in the brainstem (Shaikh et al., 2016). Once stimulated, efferent motor signals are transferred via cranial nerves V, VII, IX, X, and XII to the upper gastrointestinal (GI) tract. The lower GI tract is then stimulated via cranial nerve X and sympathetic nerves. Signals are subsequently relayed to the diaphragm and abdominal muscles via the spinal nerves initiating the act of vomiting (Hall, 2011).

**Risk Factors.** There are many risk factors that can contribute to the development of PONV. Apfel et al. (2012) conducted a systematic review in which 22 studies with a total of 95,154 patients were included. The studies were pooled together to evaluate

independent risk factors and other noncontributory factors. The researchers searched PubMed, EMBASE, and Cochrane databases for any available evidence. They did not restrict their search with any publication dates or language requirements. They also hand searched the reference lists of the studies found. Three individual investigators systematically evaluated the retrieved studies. Observational studies with more than 500 adults as well as randomized controlled trials were included. Data extraction was done by one researcher and validated by a second individual investigator (Apfel et al., 2012). Statistical analysis was performed with the Review Manager and bias in publication was evaluated for all independent predictors with statistical significance. From the cohorts, odd ratios (OR) were calculated by allotted point estimates for anesthesia related, patient-specific, and surgery related factors. There were five independent factors related to anesthesia, eight patient specific factors, and 14 surgical risk factors identified (Apfel et al., 2012).

Female gender was found to be the strongest patient-specific independent risk factor with an OR of 2.57 (Apfel et al., 2012). The second strongest was having a history of PONV and/or motion sickness (OR 2.09); followed by being a non-smoker (OR 1.82). History of migraine was also found to be significant (OR 1.77). ASA status, BMI, and age were not as significant (OR 1.21, 1.00, and 0.88 per decade, respectively) (Apfel et al., 2012). Of the anesthesia related risk factors, volatile agents were found to have the highest significance (OR 1.82). Next was the duration of anesthesia, per hour, (OR 1.46). The use of nitrous oxide followed close behind (OR 1.45). The fourth and fifth anesthesia related factors contributing to the development of PONV were the use of opioids: postoperatively (OR 1.39) and intraoperatively (OR 1.03) (Apfel et al., 2012).

The researchers identified 13 surgeries that contributed to PONV. The surgery with the highest incidence of developing PONV was a cholecystectomy (1.90). Laparoscopic and gynecologic procedures followed thereafter (OR 1.37 and 1.24, respectively). The other surgeries that did not have clinical significance are: ENT, thyroid, ophthalmologic, orthopedic, abdominal, plastic, neurological, and head and neck surgery (Apfel et al., 2012).

**Risk Assessment for PONV.** To better facilitate identification of risk factors, it is essential to assess individual patient's risks for PONV. The two most frequently used risk assessment tools for PONV are the Apfel score and the Koivuranta score (Gan et al., 2014).

The Apfel scoring system was developed after data from two independent studies were combined and cross analyzed (Apfel et al., 1999). A simplified risk score was created and cross-validated with the original scores concluding the discriminating power was not altered with the simplification. As a result, a final score was created consisting of the following four predictors: female gender, history of PONV, history of motion sickness, being a nonsmoker, and the use of opioids in the postoperative period (Apfel et al., 1999). The presence of 0, 1, 2, 3, or 4 risk factors corresponds with the incidence of PONV as 10%, 20%, 40%, 60%, and 80% respectively. Patients are scored as "low", "medium", or "high" based on the number of risk factors they have; 0 – 1, 2, or 3, respectfully (Gan et al., 2014).

The Koivuranta score was developed from a prospective interview-based survey of 1107 inpatients. Each patient received a 78-item questionnaire that accompanied them throughout their hospital stay. Information was collected regarding patient

characteristics, presumed risk factors, details regarding the anesthetic and surgical procedure, and occurrence of nausea and vomiting. The study determined the most significant factors associated with an increased incidence of nausea and vomiting were: female gender, history of PONV, extended duration of surgery, being a nonsmoker, and history of motion sickness. Thus, the Koivuranta score was developed (Koivuranta et al., 1997).

In a study done by van den Bosch et al. (2005) to validate the Apfel and Koivuranta scoring systems, 1388 adult patients undergoing a variety of surgical procedures were screened. The prognostic accuracy of each scoring system was evaluated based on prediction of developing one episode of nausea and/or vomiting within 24 hours postoperatively. This study determined that both scoring systems, based on calibration and discrimination, were less accurate than anticipated compared to previous studies. According to van den Bosch et al. (2005), both risk assessments provided too extreme of prediction. Apfel's area under the Receiver Operating Characteristic curve (ROC area) was 0.63 and Koivuranta's ROC area was determined to be 0.66. The ROC area can range from discrimination equal to that of chance (0.5) to perfect discrimination (1.0). These numbers are considerable, especially related to over treatment, which can expose patients to unnecessary side-effects. This can be detrimental in diabetic patients treated with dexamethasone if hyperglycemia ensues: poor wound healing, dehydration, hyperosmolar states and increased risk of infection (Joshi et al., 2010).

**Management of PONV.** The management of PONV requires an individualized approach to each patient in which medical history, risk factors, cost-effectiveness must be

considered. In 2014, SAMBA published consensus guidelines for the management of PONV, highlighting the importance of combination therapy for PONV prophylaxis. It is noted in the statement that combination regimens with optimal dosing have yet to be established, however, the statement did include two algorithms based on individualized risk factors (Gan et al., 2014). Each algorithm has suggestions for prophylactic interventions and treatment of PONV. A risk assessment is conducted first for each patient using either Koivuranta or Apfel scoring tool. Next, depending on provider preference of implementing prophylactic measures, interventions are made based on patients identified risk category. The first table (Table 1) does not provide an intervention for patients identified as "low-risk". For "medium-risk" patients, a two-drug combination is recommended for prophylaxis; and a three-drug combination for "high-risk" patients. The second table (Table 2) provides prophylactic intervention for all patients regardless of risk. Gan et al. (2014) does stress the drugs suggested for use in each table are examples of interventions that could be used, however each patient's treatment plan must be individualized.

**Table 1**

*Risk-Adapted PONV-Prevention Algorithm (With No Prevention in Low-Risk Patients)*

| Estimated risk for PONV, as determined by a risk score | | | |
|---|---|---|---|
| | **Low** | **Medium** | **High** |
| Interventions for prophylaxis | No preventions ("wait and see") | Drug A + Drug B or TIVA | Drug A + Drug B + TIVA<br><br>On a case -by-case decision: further interventions |
| Interventions for treatment | 1. Drug B<br>2. Drug C (in case of ineffectiveness of treatment in stage 1) | 1. Drug C<br>2. Drug D (in case of ineffectiveness of treatment in stage 1) | 1. Drug C<br>2. Drug D (in case of ineffectiveness of treatment in stage 1) |

*Note.* Example interventions for adult patients: Drug A = dexamethasone 4mg; Drug B = ondansetron 4mg; Drug C = droperidol 1mg; Drug D = dimenhydrinate 1mg/kg. TIVA = total intravenous anesthesia i.e. propofol induction and maintenance, without use of nitrous oxide (Gan et al., 2014).

**Table 2**

*PONV-Prevention Algorithm in All Patients Including Low-Risk Patients Plus Additional Interventions for High-Risk Patients*

| Estimated risk for PONV, as determined by a risk score | | | |
|---|---|---|---|
| | **Low** | **Medium** | **High** |
| Interventions for prophylaxis | Drug A + (Drug B or TIVA) | Drug A + (Drug B or TIVA) | Drug A + Drug B + TIVA<br>On a case -by-case decision: further interventions |
| Interventions for treatment | 1. Drug C2. Drug D (in case of ineffectiveness of treatment in stage 1) | 1. Drug C<br>2. Drug D (in case of ineffectiveness of treatment in stage 1) | 1. Drug C<br>2. Drug D (in case of ineffectiveness of treatment in stage 1) |

*Note.* Example interventions for adult patients: Drug A = dexamethasone 4mg; Drug B = ondansetron 4mg; Drug C = droperidol 1mg; Drug D = dimenhydrinate 1mg/kg. TIVA = total intravenous anesthesia i.e. propofol induction and maintenance, without use of nitrous oxide (Gan et al., 2014).

A randomized, controlled trial was completed in 2004 by Apfel et al., in which 5,199 patients were enrolled for evaluation of treatment for postoperative nausea and

vomiting. The trial was of factorial design in which as many as three antiemetic interactions were evaluated. Of the patients enrolled, 4,123 subjects were randomly allocated to 1 of 64 prophylactic interventions: no ondansetron or 4mg of ondansetron; no dexamethasone or 4mg of dexamethasone; no droperidol or 1.25mg of droperidol; volatile anesthetic or propofol; nitrous oxide or nitrogen; fentanyl or remifentanil. The other patients were randomly assigned to one of the four first interventions (Apfel et al., 2004). Nausea and vomiting 24 hours postoperatively were the primary outcome, measured blindly. The study concluded dexamethasone, droperidol, and ondansetron independently reduced the risk of PONV by approximately 26%. A 19% reduction in risk was observed with the use of propofol and a 12% reduction with the use of nitrogen. The combination of nitrogen and propofol (TIVA) were similar to the other antiemetics, when used independently. The authors concluded that due to the variety of mechanisms of actions of each antiemetic and similar effectiveness, the first choice should be based on patient profile or the most cost-effective intervention. They also reported low risk patients rarely need prophylaxis, a single intervention may be beneficial in patients with moderate risk and high-risk patients should have multiple interventions (Apfel et al., 2004).

In a meta-analysis done by Henzi et al. (2000) the use of dexamethasone for the prevention of PONV was conducted using data from 17 trials with 1,946 patients (children and adults). Analysis of the data revealed: 598 patients received dexamethasone, 582 patients received either ondansetron, granisetron, droperiodol, metoclopramide or perphenazine, 423 patients received a placebo; and 343 received a combination of dexamethasone with either ondansetron or granisetron. With placebo, the

incidence of early PONV (0 to 6 hours postoperatively) was 35%, and late PONV (0 to 24 hours postoperatively) was 50%. In order to prevent early and late vomiting in adult patients, the researchers found 7.1 (95% CI 4.5 to 18) and 4.3 (2.3 to 2.6) was the number needed to treat, respectively (Henzi et al., 2000). In examining the combination of dexamethasone with a 5-$HT_3$ receptor antagonist: ondansetron or granisetron, the number needed to treat was 7.7 (4.8 to 19) compared to the 5-$HT_3$ receptor antagonist alone at 7.8 (4.1 to 66). The data from the other antiemetic options were deemed incomparable and therefore inconclusive. The researchers concluded the most optimal prophylactic treatment regimen to prevent PONV in healthy patients was with a combination of dexamethasone and a 5-$HT_3$ receptor antagonist (Henzi et al., 2000).

The prophylactic management of PONV in diabetic surgical patients can be complicated especially when the use of dexamethasone is widely popular. SAMBA's consensus statement regarding the management of *diabetic* patients undergoing *ambulatory surgery* published in 2010 approves of the use of dexamethasone 4mg for prophylactic treatment of PONV (Joshi et al., 2010). However, in 2014, SAMBA's consensus statement on the *management of PONV* undergoing *ambulatory surgery* reports conflicting evidence regarding dexamethasone dosing and implications on BG levels. This consensus statement reports dexamethasone use is relatively contraindicated in labile diabetic patients (Gan et al., 2014). This current systematic review examines the data regarding these statements and further evaluates the effects of dosing, 4mg or 8mg, of dexamethasone on blood sugars postoperatively.

**Pharmacologic Antiemetic Classifications**

**Dopamine Antagonists.** The two main dopamine antagonists are metoclopramide and droperidol; however, haloperidol and perphenazine also used. Metoclopramide promotes gastric motility, increases gastroesophageal sphincter tone, and relaxes the pylorus and duodenum. It is also an antidopaminergic, with its ability to cross the BBB and act on the CRTZ. However, due to its extrapyramidal side effects, it is not used as frequently. Droperidol is a well-established antiemetic exerting its effects on the GABA receptors in the CRTZ zone. This drug, however, has become controversial since acquiring a black box warning for association of patients developing torsades de pointes or severe arrhythmias due to QT prolongation (Miller et al., 2015).

Haloperidol is another dopamine agonist that is used as an antiemetic. Haloperidol acts on the CRTZ and has been used commonly for nausea and sickness caused by chemotherapy. It also has peripheral GI effects by relaxing the gastric sphincter (Miller et al., 2015). Perphenazine is also a dopamine antagonist that is known for its highly potent neuroleptic effect (Miller et al., 2015).

**Histamine Antagonists.** Two common antihistamines are meclizine and promethazine. Both of these drugs antagonize histamine receptors. They also exert effects on the vestibular apparatus by blocking acetylcholine receptors. Another uncommon antihistamine used is, dimenhydrinate. This drug acts on the $H_1$ receptor and also has weak antimuscarinic activity. It has been used for the treatment of motion sickness (Miller et al., 2015).

**Anticholinergic Antagonists.** Transdermal scopolamine exerts its effects on the vestibular nuclei by inhibiting cholinergic transmission. It also works on the

parasympathetic nervous system by way of competitive inhibition of muscarinic receptors. It is used primarily for patients with a history of motion sickness.

**Serotonin Antagonists.** Agents such as ondansetron, dolasetron, palonosetron, and granisetron are 5-HT antagonists that act centrally and also block vagal afferents located in the gut.

**Neurokinin- 1 Receptor (NK-1) Antagonists.** Aprepitant, Cospitant, and Rolapitant are part of a new group of antiemetics. Their mechanism of action is blocking NK-1 receptors located in the NTS and areas in the reticular formation (Shaikh et al., 2016).

**Propofol.** Propofol is a hypnotic-sedative that is frequently used for the induction and maintenance of general anesthesia. It is also used in conjunction with regional anesthesia, local anesthesia, and for monitored anesthesia care. It exerts its effects by increasing chloride conductance at the $GABA_a$ receptor. Propofol has been found to have anti-emetic properties and its use is recommended for reducing the baseline risk of developing PONV. Sub-hypnotic doses of propofol have also been studied independently for antiemetic properties (Gan et al., 1997).

**Dexamethasone.** The corticosteroid dexamethasone provides an antiemetic effect by inhibiting the NTS in addition to inhibiting the synthesis of prostaglandins. The blocking of prostaglandin synthesis results in better emesis control due to its effect on the sensitization of emesis controlling neurotransmitters (Shaikh et al., 2016). In a study performed by Wang et al. (2000) the minimum effective dose of dexamethasone was examined in women undergoing a thyroidectomy. Two hundred seventeen women were enrolled in a randomized, double-blinded, placebo-controlled study in which

dexamethasone was administered at 10mg, 5mg, 2.5mg, 1.25mg, or saline. The results concluded that the minimum effective dose of dexamethasone for preventing PONV is 5mg and there were no significant differences between the groups receiving 10mg doses compared to 5mg doses. This finding can be clinically significant in mitigating the side effects associated with the use of dexamethasone.

***Additional uses for dexamethasone.*** The use of corticosteroids, specifically dexamethasone, has been shown not only to be efficacious as an antiemetic, it has also been shown to be successful in treating post-operative pain. A randomized, double-blind, placebo-controlled study performed by Kardash et al. (2008) aimed to analyze the effects of single-dose dexamethasone prior to total hip arthroplasty on dynamic pain. Prior to surgery, fifty patients receiving propofol sedation with spinal anesthesia were placed into two groups: group 1received 40mg of dexamethasone and group 2 received IV saline. Postoperative pain was measured with the 0-10 numeric rating scale (NRS) every 4 hours for 48 hours. The results elicited a reduction is dynamic pain in group 1 (NRS score: 2.7, 95% CI: 2.2-3.1 vs 6.8, 6.4-7.2; $p< 0.0001$). They also noted there was no morphine consumption or significant pain at rest at any given time. Of note, seven patients from the control group were treated for nausea compared to only one from group 1 (Kardash et al., 2008). The researchers also measured an anti-inflammatory marker, C-reactive protein, in a subgroup of 25 patients 48 hours postoperatively. They concluded patients who received dexamethasone had markedly reduced levels of C-reactive protein (52.4 mg/mL, 28.2-76.6 vs 194.2, 168.9-219.4; $p < 0.0001$) (Kardash et al., 2008).

As the above study notes, dexamethasone has been used as an anti-inflammatory. Usage of dexamethasone has been shown to decrease prostaglandin production by

inhibiting cyclooxygenase type II, phospholipase and other major cytokines including C-reactive protein, tumor necrosis factor (TNF), and several interleukins (IL) (Nagelhout & Plaus, 2014). In a study done by el Azab et al. (2002) nine out of seventeen patients (group 1) undergoing cardiopulmonary bypass received dexamethasone 100mg before anesthesia induction. The eight other patients were placed in the control group (group 2). Perioperative plasma levels were measured for TNF, IL-4, IL-6, IL-8, and IL-10. Postoperatively it was concluded that IL-8 and TNF did not significantly increase in group 1 as compared to group 2 which had a greater increase than the preoperative values ($p < 0.05$). Both groups had an increase in IL-6; However, group 1 had less of an increase compared to group 2 ($p < 0.05$). Group 1 had a higher increase of IL-10 compared to group 2 ($p < 0.05$). Finally, group 2 had a decrease in IL-4, however it did not change in group 1 ($p < 0.05$) (el Azab et al., 2002). Of note postoperatively, group 2 did have hyperthermia, tachycardia, increased pulmonary artery pressure, increased respiratory rate, and a more prolonged stay in the intensive care unit. Despite the low number of participants, the authors concluded from their study that postoperative outcomes may improve from dexamethasone use prior to cardiac surgery due to the anti-inflammatory effect on circulating cytokines (el Azab et al., 2002).

Steward et al. (2011) account that there have not been any adverse effects from a single dose of dexamethasone. However, Nalgelhout & Plaus (2014), claim a transient increase in blood glucose levels can be appreciated after the administration of dexamethasone. However, a momentary increase in BG level for a diabetic may negatively impact health outcomes. Patients with hyperglycemia during the surgical period are at a greater risk for electrolyte imbalances, dehydration, increased risk of

infection, fluid shifts, compromised wound healing, and ketoacidosis (Joshi et al., 2010). Despite it's proven anti-inflammatory effects and anti-pain properties, the use of dexamethasone in the diabetic population has been controversial related to the degree of BG fluctuation. This systematic review examines more recent studies to determine the extent in which dexamethasone effects BS in the diabetic patient.

Next, the theoretical framework will be presented.

## Theoretical Framework

A guide for evaluating systematic reviews was identified by Moher et al. in 2009. They articulated that a systematic review incorporates "a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (Moher et al., 2009, p. 264). This process is of utmost importance for health care workers due to many policies, practices, and further research are guided by systematic reviews. In order to guide this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) theoretical framework will be used.

The PRISMA theoretical framework has a 27-point checklist to guide the researcher through critical appraisal of each RCT to be used. This ensures an analytical and unbiased evaluation is made of each RCT. The checklist provides the researcher with a step-by-step guide for examining the RCT, including their introduction, methods, results, and discussion. Once the initial research has been conducted, PRISMA uses a flow diagram to elicit the extent of the search. The four phases consist of identification, screening, eligibility, and studies included. This allows the researcher to present the extent of their search and screening process for their systematic review (Moher et al., 2009).

In order to facilitate an unbiased, thoroughly conducted systematic review, the use of PRISMA will be implemented when examining the use of dexamethasone in adult diabetic surgical patients to prevent PONV and the impact on blood glucose levels.

Next, the methods will be presented.

# Methods

## Purpose

The purpose of this study was to examine the use of dexamethasone and the impact on blood glucose levels for the prevention of PONV in adult diabetic surgical patients. In order to thoroughly examine this issue, a systematic review of multiple randomized control trials was completed.

## Inclusion/Exclusion Criteria

Inclusion criteria for the studies included: (a) adults 18 years of age and older, (b) patients undergoing surgery, (c) the use of dexamethasone for PONV, (d) patients with the diagnosis of diabetes mellitus type I or type II. Exclusion criteria for the studies included: (a) pediatric patients, (b) gestational diabetic patients.

## Search Strategy

A detailed search was performed using CINAHL (Cumulative Index to Nursing and Allied Health Literature) and MEDLINE. Keywords utilized were: "dexamethasone" AND "diabet*" AND "postoperative nausea and vomiting" OR "PONV". Restrictions of English language and human subjects were implemented to the search.

## Data Collection

Data collected from each study included: study purpose, design, and location; number of subjects included, type of surgery; baseline, intraoperative, and postoperative blood glucose levels; along with dexamethasone dosage and the use of placebo and/or other anti-emetic pharmacologic treatment.

## Critical Appraisal

Literature collected was critically appraised using *Critical Appraisal Skills Progamme* (CASP). CASP (Table 3) combines a three-step approach and a checklist to guide the researcher in ensuring validity when synthesizing research (Critical Appraisal Skills Programme, 2017). After completion of each study evaluation and summary a comprehensive cross study analysis was completed.

**Table 3**

*Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist.*

| **A. Are the results of the trial valid?** | **Yes** | **Can't tell** | **No** |
|---|---|---|---|
| 1. Did the trial address a clearly focused issue? | | | |
| 2. Was the assignment of patients to treatments randomized? | | | |
| 3. Were all of the patients who entered the trial properly accounted for at its conclusion? | | | |
| 4. Were patients, health workers, and study personnel "blind" to treatment? | | | |
| 5. Were the groups similar at the start of the trial? | | | |
| 6. Aside from the experimental intervention, were the groups treated equally? | | | |
| **B. What are the results?** | **Yes** | **Can't tell** | **No** |
| 7. How large was the treatment effect? | | | |
| 8. How precise was the estimate of the treatment effect? | | | |
| **C. Will the results help locally?** | **Yes** | **Can't tell** | **No** |
| 9. Can the results be applied in your context? | | | |
| 10. Were all clinically important outcomes considered? | | | |
| 11. Are the benefits worth the harms and costs? | | | |

*Note:* CASP checklist completed on all studies that met inclusion criteria.

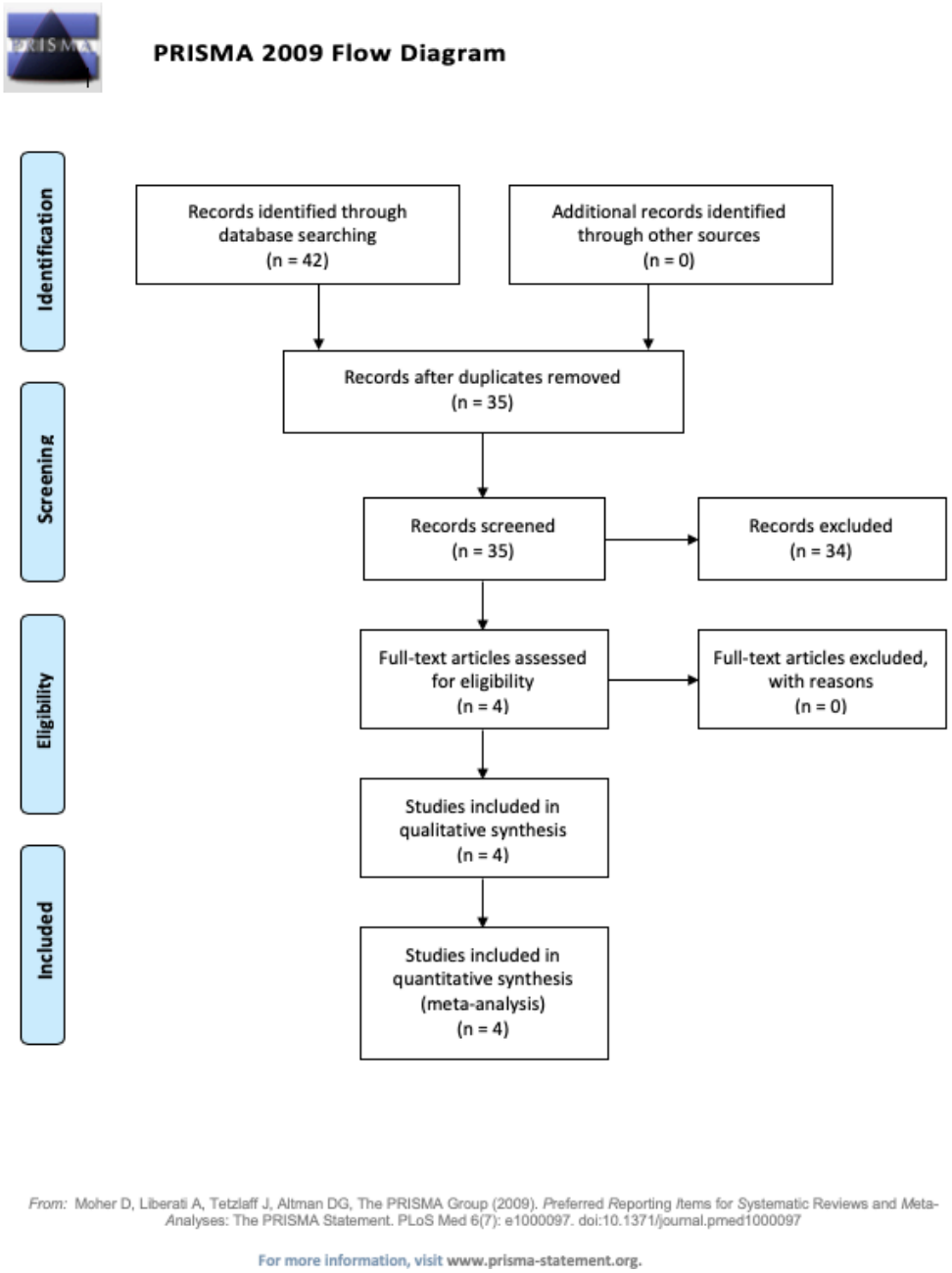
**Data Synthesis & Cross Study Analysis**

Upon completion of each individual study evaluation and summary a comprehensive cross study analysis was completed. The cross-study analysis compared dexamethasone dosing, use of placebo or other anti-emetic pharmacologic treatment, and the evaluation of baseline, intraoperative, and postoperative blood glucose levels. Next, the results will be presented.

## Results

**Figure 1**

*Completed PRISMA flow diagram demonstrating article identification, screening, eligibility, and inclusion (Moher et al., 2009).*



The completed PRISMA flow diagram as depicted in Figure 1 illustrates a visual analysis of how the four final studies were gathered to complete this systematic review. An initial search of the selected databases, CINAHL and MEDLINE, was completed using the search term "dexamethasone", resulting in 72,395 studies. The addition of search term "diabet*" narrowed the results to 2,520 studies. By adding "postoperative nausea and vomiting" OR "PONV" to the search field, the results were narrowed down to 35 studies. A total of seven articles were excluded due to duplication. After article screening, 31 studies were excluded due to failing to meet previously identified inclusion criteria. Lastly, the remaining four studies were appraised and chosen to complete this systematic review to examine the use of dexamethasone and the impact on blood glucose levels for the prevention of PONV in adult diabetic surgical patients.

Each of the four studies selected and appraised for this systematic review include a description of the results with applicable study findings identified. Appendix A (Tables A1 – A4) depicts study specific data that was collected for each individual study. Each individual table includes the following key information: purpose of the study, study design, location, sample make up, methods used, and surgical procedure performed. Following is Appendix B (Tables B1 – B4) which lists the outcome data that was collected. Study specific findings include: BG sample times, baseline BG reading, mean peak BG levels and maximum BG levels. Each table does have a degree of individualization due to variance in each study. Next, Appendix C (Tables C1 – C4) lists the critical appraisal data tables of individual studies that were created to assess the legitimacy, consistency, and applicability through a three-part, 11 question series.

Finally, Appendix D, a cross-study analysis data table was created to assist in comparing the results of each individual study.

**Individual Studies**

The single-center, prospective, double-blind randomized trial by Nazar et al. (2009) (Appendix A – 1) investigated the effect of administering dexamethasone in the perioperative period on patients with poor glycemic control undergoing laparoscopic Roux-en-Y gastric bypass surgery. A total of 30 obese patients (BMI >35kg/$m^2$) with impaired glucose tolerance were randomly divided into two groups. Group 1, the dexamethasone group consisted of 15 participants while the remainder 15 participants compromised group 2, the control group. Group 1 received dexamethasone 8mg IV immediately after induction of anesthesia, while Group 2 received 2ml of isotonic saline IV at the same designated time. Standardized surgical technique, per institution protocol, was followed and the participants received a total gastroplasty with gastric pouch (30ml) with 150 cm exclusion of small intestine and gastrojejunal anastomosis. Baseline BG level was obtained preoperatively with IV placement. BG levels were reassessed every two hours after surgical start for 12 hours. A difference of 45 mg/dl in peak glucose values between groups was considered statistically significant. The BG levels were not corrected during the study.

Outcomes of this study by Nazar et al. (2009) (Appendix B – 1) concluded that all BG samples measured after the beginning of surgery were higher compared to baseline in both groups. Group 1, the dexamethasone group, exhibited higher BG levels from the 6$^{th}$ to the 12$^{th}$ hour after anesthesia compared to the control group. Group 2 maximum BG

levels were found to be significantly different compared to Group 1 (Group 1: M = 187.2 versus Group 2: M = 158.4) (*p*-value <0.05) (Nazar et al., 2009).

When assessing the integrity of the study using the CASP questionnaire (Appendix C, Table C – 1), the trial addressed a clearly focused issue in which all of the participants were randomized to treatment and it was also noted that study personnel, participants, healthcare workers were "blind" to treatment. Both groups were similar at the start of the trial, treated equally aside from the experimental intervention, and all of the participants were accounted for at the end of the trial. The results can be applied to diabetics undergoing surgical procedures however the study is limited due to the small number of participants (Nazar et al., 2009). Due to a hyperglycemia having an impact on wound healing and infection rates, this study did not examine all clinically important outcomes (Guvener et al., 2002). As a result, it is inconclusive whether the benefits outweigh the risks.

This single -center, placebo-controlled study by Abdelmalak et al. (2013) was randomized to dexamethasone or placebo and stratified by the presence or absence of diabetes (Appendix A, Table A-2). The patients were part of a larger underlying study in which they were randomized to either tight glucose control with a target plasma concentration of 80 to 110 mg/dl or conventional glucose control of 180 to 200 mg/dl, regardless of diabetic status: The Dexamethasone, Light Anesthesia and Tight Glucose Control [DeLiT] Trial (Abdelmalak et al., 2013). This study's purpose was to investigate the change of blood glucose, from preoperative to maximal intraoperative, after administration of dexamethasone 8mg IV to diabetic and nondiabetic patients undergoing noncardiac surgery under general anesthesia. A total of 185 patients ≥ 40 years of age,

restricted to the conventional glucose group, were divided into four groups. Group 1 consisted of 21 diabetic patients who received dexamethasone 8mg IV 1-2 hours prior to incision, Group 2 comprised of 28 diabetic patients who received a placebo, Group 3 consisted of 69 nondiabetic patients who received dexamethasone 8mg IV 1-2 hours prior to incision, and Group 4 comprised 67 nondiabetic patients who received a placebo. Fasting BG levels were obtained preoperatively. A mean group difference of ≥ 28 mg/dl signified clinical relevance. Insulin was given when BG levels were >215 mg/dl to maintain target range of 180 to 200 mg/dl. Baseline BG was assessed preoperatively and then reassessed at least hourly when stable and every 30 minutes after intervention. *Stable* BG was defined by Abdelmalak et al. (2013) as a BG < 215 which required no intervention such as insulin bolus or adjustment of insulin infusion, with two consecutively similar BG readings. *Interventions* included insulin boluses or adjustment of insulin infusion rate. All patients received a general anesthetic with sevoflurane in air and oxygen for a noncardiac surgery in addition to a standardized infusion of IV fentanyl (Abdelmalak et al., 2013).

Outcomes of this study by Abdelmalak et al. (2013) (Appendix B, Tables B – 2.1-2) demonstrated the mean maximal BG change did not change significantly between the diabetic and nondiabetic patients ($p$=0.39). Dexamethasone increased the mean maximal BG change compared to control in nondiabetic patients (Group ND1: M = 86mg/dl, versus Group ND2: M = 58mg/dl) ($p$=0.0012). However, there wasn't a hyperglycemic response to dexamethasone observed in diabetic patients (Group DM1: M = 63mg/dl versus Group DM2: M = 63mg/dl), ($p$=0.99) (Abdelmalak et al., 2013).

When assessing the integrity of the study using the CASP questionnaire (Appendix C, Table C – 2), the trial addressed a clearly focused issue in which all of the participants were randomized to treatment and it was also noted that study personnel, participants, healthcare workers were "blind" to treatment. The groups were not similar at the start of the trial, diabetic patients were outnumbered 49 compared to 136. Also, interventions were implemented aside from the experimental intervention for patients with BG >215mg/dl. All of the participants were accounted for at the end of the trial. The results can be applied to patients undergoing surgical procedures however the study is limited due to treatment received when BG >215mg/dl (Abdelmalak et al., 2013). Due to a hyperglycemia having an impact on wound healing and infection rates, this study did not examine all clinically important outcomes (Guvener et al., 2002). As a result, it is inconclusive whether the benefits outweigh the risks.

The single-center, prospective, randomized trial by Tien et al. (2016) (Appendix A, Table A – 3) investigated the effect of prophylactic administration of dexamethasone or ondansetron for prevention of postoperative nausea and vomiting and the effects on blood glucose levels in non-diabetic and type-2 diabetic surgical patients. A total of 85 adult English-speaking patients scheduled for a general anesthetic elective surgery anticipated to last >1 hour and expected to be admitted to the hospital for at least 24 hours were divided into 4 groups. Group 1 consisted of 20 non-diabetic participants who received dexamethasone 8mg IV at induction of anesthesia, Group 2 comprised 21 non-diabetic participants who received 4mg ondansetron IV towards the end of the procedure, Group 3 consisted of 20 type 2 diabetic patients who received dexamethasone 8mg IV at induction of anesthesia, and Group 4 comprised 24 type 2 diabetic patients who received

ondansetron 4mg IV towards the end of the procedure. Baseline BG was obtained preoperatively and sent to the central laboratory for measurement. A mean increase in BG levels by 30.6 mg/dl was to be considered significant. Additional BG samples were sent at set time intervals: 2 hours, 4 hours, and 24 hours. A variety of surgical procedures were preformed and classified into the following groups: open gynaecological, laparoscopic gynaecological, open abdominal, laparoscopic abdominal, or other (Tien et al., 2016).

Outcomes of this study by Tien et al. (2016) (Appendix B, Table B – 3) demonstrated in non-diabetic patients, the maximum BG was higher in those who received dexamethasone compared to those who received ondansetron ($p = 0.04$); the same conclusion was exhibited with type 2 diabetic patients who received dexamethasone compared to those who received ondansetron ($p < 0.01$).

When assessing the integrity of the study using the CASP questionnaire (Appendix C, Table C – 3), the trial addressed a clearly focused issue in which all of the participants were randomized to treatment and it was also noted that study personnel, participants, healthcare workers were "blind" to treatment. The groups were not similar at the start of the trial, patients selected for the study were diabetic and non-diabetic, of varying age, and received various types of surgery. Also, an intervention of subcutaneous insulin was implemented aside from the experimental intervention for diabetic patients whose BG levels > 200 mg/dl. All of the participants were not accounted for at the end of the trial, three out of 88 patients were discharged early from the hospital and considered lost to follow-up. The results can be applied to patients undergoing surgical procedures however the study is limited due to treatment received

when BG >200mg/dl (Tien et al., 2016). Due to a hyperglycemia having an impact on wound healing and infection rates, this study did not examine all clinically important outcomes (Guvener et al., 2002). As a result, it is inconclusive whether the benefits outweigh the risks.

The final study included in this systematic review is a single-center, prospective, placebo-controlled randomized trial by Purushothaman et al. (2018) (Appendix A, Table A – 4) investigated the effect of administering two low doses (4mg or 8mg) of dexamethasone on BG levels of diabetic and nondiabetic patients receiving spinal anesthesia for elective surgeries. A total of 180 elective surgical patients aged 18 – 70 years undergoing spinal anesthesia were divided into six groups: group 1, the diabetic control group consisted of 30 patients; group 2, consisted of 30 diabetics who received dexamethasone 4mg IV immediately prior to delivery of spinal anesthetic; group 3, consisted of 30 diabetics who received dexamethasone 8mg IV immediately prior to delivery of spinal anesthetic; group 4, the nondiabetic control group consisted of 30 patients; group 5, consisted of 30 nondiabetics who received dexamethasone 4mg IV immediately prior to delivery of spinal anesthetic; and group 6, consisted of 30 nondiabetics who received dexamethasone 8mg IV immediately prior to delivery of spinal anesthetic. Baseline capillary BG level was obtained immediately prior to administration of dexamethasone or control and reassessed every hour for 7 hours. A mean BG change of 23 mg/dl was to be considered clinically significant. The test drugs were reconstituted to a volume of 5mls and given immediately prior to delivery of spinal anesthetic. A standardized spinal anesthetic was followed using aseptic technique – a 25-gauge Quincke needle was used to deliver 0.5% hyperbaric bupivacaine 15mg and

buprenorphine 60 mcg at either L2-L3 or L3-L4 midline approach. A total of 133 general surgeries, 24 gynecologic, and 43 orthopedic/plastic and other surgeries were included (Purushothaman et al., 2018).

Outcomes of this study by Purushothaman et al. (2018) (Appendix B, Table B – 4.1-2) demonstrated that there was a rise in BG levels in both diabetic and nondiabetic groups who received dexamethasone. However, this rise was not clinically significant with a range of 10-15 mg/dl from baseline. Blood glucose levels peaked at 240 minutes in group 2, the diabetic group that received 4mg dexamethasone IV, which was a statistically significant increase from baseline. Blood glucose levels in the group 3, the diabetic group that received 8mg dexamethasone IV peaked at 300 minutes. Blood glucose levels peaked in the group 5, the nondiabetic group that received dexamethasone 4mg IV, and group 6, the nondiabetic group that received dexamethasone 8mg IV, at 300 minutes and 360 minutes, respectively. At 480 minutes, in comparison with the group 3, group 6 had a statistically significant increase in BG levels (Purushothaman et al., 2018).

When assessing the integrity of the study using the CASP questionnaire (Appendix C, Table C – 4), the trial addressed a clearly focused issue in which all of the participants were randomized to treatment and it was also noted that study personnel, participants, healthcare workers were "blind" to treatment. The groups were not similar at the start of the trial due to a variety of surgical procedures being performed. However, the groups were treated equally aside from the experimental intervention, and all of the participants were accounted for at the end of the trial. The results can be applied to diabetics undergoing surgical procedures however the study is limited due to the participants received a spinal anesthetic which is different compared to all of the other

studies who received a general anesthetic (Purushothaman et al., 2018). Due to a hyperglycemia having an impact on wound healing and infection rates, this study did not examine all clinically important outcomes (Guvener et al., 2002). As a result, it is inconclusive whether the benefits outweigh the risks.

**Cross-Study Analysis**

The cross-study analysis table (Appendix D) exhibits the PONV prophylaxis used for each study, as well as the major outcomes investigated including: Mean BG at 2 hours, 4 hours, 6 hours, and 8 hours; as well as mean peak BG levels. Each study had a varying time frame in which BG samples were measured. Nazar et al. (2009) measured mean BG at all of the above time frames mentioned. Abdelmalak et al. (2013) did not list any BG levels for their four groups, instead listed overall mean peak BG levels. Tien et al. (2016) listed mean BG for 2 hours, 4 hours and mean peak BG. Purushothaman et al. (2018) listed all of the mean BG at all of the above time frames mentioned.

All studies included dosing of dexamethasone 8mg IV in diabetic patients and was compared against a diabetic control (study 1, 2, and 4), a nondiabetic control (study 2 and 4), nondiabetic patients receiving dexamethasone 8mg IV (study 2 and 4), nondiabetic and diabetic patients receiving ondansetron 4mg IV (study 3) and nondiabetic and diabetic patients receiving dexamethasone 4mg IV (study 4). There was an increase in mean peak BG in diabetic patients receiving dexamethasone 8mg IV compared to diabetic control in study 1 and 4, however it was only clinically significant in study 1 ($p<0.05$). In study 2 there was not a change in mean peak BG in the diabetic patients receiving dexamethasone 8mg IV compared to the diabetic control group (Group DM1: M = 209mg/dl versus Group DM2: M = 209mg/dl). There was an increase in

mean peak BG in diabetic patients receiving dexamethasone 8mg IV compared to the nondiabetic control group in study 2 (Group DM1: M = 209mg/dl versus Group ND2: M = 154mg/dl) and study 4 (Group DM3: M = 168mg/dl versus Group ND4: M = 105mg/dl). In the diabetic groups receiving dexamethasone 8mg IV, there was a small increase in BG compared to nondiabetic patients receiving dexamethasone 8mg IV in study 2 (Group DM1: M = 209mg/dl versus Group ND1: M = 182mg/dl) and study 4 (Group DM3: M = 168mg/dl versus Group ND6: M = 140mg/dl). In study 3, the diabetic group receiving dexamethasone 8mg IV had an overall increase in mean peak BG compared to the diabetic group receiving ondansetron (Group DM3: M = 252mg/dl versus DM4: M = 192.6 mg/dl). There was also an increase in BG in the diabetic group receiving dexamethasone 8mg IV compared to both nondiabetic groups receiving either dexamethasone or ondansetron, respectively (Group DM3: M = 252mg/dl versus Group ND1: M = 163.8mg/dl versus Group ND2: M = 140.4mg/dl). In study 4, the diabetic group receiving dexamethasone 8mg IV had an increase in mean peak BG compared to the nondiabetic group that received dexamethasone 4mg IV (Group DM3: M = 168mg/dl versus Group ND5: M = 133mg/dl). However, when the diabetic group receiving dexamethasone 8mg IV is compared to the diabetic group receiving dexamethasone 4mg IV, the latter group has a higher BG (Group DM3: M = 168mg/dl versus Group DM2: M = 169mg/dl).

Next, the summary and conclusions will be presented.

## Summary and Conclusions

In the United States, DM is the sixth most common cause of death, with severe implications on other leading causes of mortality: cardiovascular and cerebrovascular disease (Coursin et al., 2004). The incidence of type 2 DM far outweighs type 1 with 8-10% of all Americans or 95% of all diabetics having type 2. This number is projected to double in the United States within the next several decades, affecting a third to a quarter of the population (Coursin et al., 2004). This has significant implications for the health care system when there is an 18 – 22 year loss of estimated quality adjusted life years for patients with a diagnosis of diabetes. Along with a loss of years lived, diabetics undergo an increased amount of surgeries and procedures, necessitate more hospitalizations, longer lengths of stay, and at greater cost compared to nondiabetic patients (Coursin et al., 2004). As an independent risk factor for poor outcomes, hyperglycemia in the perioperative period becomes a major concern for the anesthetist. Many type 2 diabetics fail to be diagnosed until the time of their procedure or illness, with as many as 50% of patients developing significant end organ compromise prior to diagnosis. The majority of diabetic patients over the age of 65 have significant asymptomatic or symptomatic coronary artery disease, in which the development of autonomic neuropathy increases the incidence of silent ischemia (Coursin et al., 2004). Diabetics with autonomic neuropathy have an increased risk of PONV and aspiration related to delayed gastric emptying. Aspiration is the leading cause of mortality in anesthesia prompting serious consideration and planning during the perioperative period (Robinson & Davidson, 2014).

Independently, PONV is the second most common complaint occurring in 20 to 40% of all surgical patients (Cao et al., 2017). The occurrence of PONV can prolong

recovery, delay discharge, and result in unanticipated hospital admission (Shaikh et al., 2016). Diabetic patients already have increased rates of hospitalizations and complications; coupled with autonomic neuropathy contributing to PONV, a strategic plan must be implemented to provide the safest anesthetic.

One of the most extensively used anti-emetics in the perioperative period is dexamethasone, a glucocorticoid. The use of dexamethasone has been associated with potential risks including impaired wound healing, increased blood glucose levels, and an increase risk of infection (Miller et al., 2015). These risk factors, combined with independent risk factors related to diabetes, make its use in the diabetic population controversial.

The purpose of this systematic review was to examine the impact of dexamethasone on blood glucose levels in the adult diabetic surgical patient when used in the prevention of PONV. A comprehensive literature review was completed using PubMed, Medline, CINAHL, and google scholar focusing on the pathology of diabetes and postoperative nausea and vomiting, and the pharmacology of dexamethasone. The theoretical framework used for this systematic review was PRISMA, a four-phase flowchart compromised of 27-item checklist. This checklist ensured an analytical and unbiased evaluation was made of each RCT (Moher et al., 2009).

Upon narrowing down the search results, individual study analysis was conducted on four studies that met the inclusion criteria. Key information from each study was incorporated into individualized study data tables. Data outcome tables were then developed to analyze the effect of dexamethasone on perioperative blood glucose of diabetic surgical patients. Following, the Critical Appraisal Skills Programme (CASP)

checklist was used to appraise the individual RCTs. Finally, a cross study analysis table was developed comparing the mean BG at 2 hours, 4 hours, 6 hours, 8 hours, and mean peak BG levels. Diabetic patients receiving dexamethasone 8mg IV were compared to a diabetic control; a nondiabetic control; nondiabetic patients receiving dexamethasone 8mg IV; nondiabetic and diabetic patients receiving ondansetron 4mg IV; and nondiabetic and diabetic patients receiving dexamethasone 4mg IV.

There were several limitations recognized when completing this systematic review. Each study had a diabetic group that received dexamethasone 8mg IV which was used for comparison, however, the remaining groups all varied amongst the individual studies. Three out of four studies had diabetic control groups with two of those studies also including nondiabetic control groups. One study failed to have a control group, comparing BG levels with diabetic and nondiabetic patients who received a different antiemetic, ondansetron 4mg IV. Only one of the studies was performed on patients who received the same surgical procedure, a laparoscopic Roux-en-Y gastric bypass. Two of the other studies had varying surgical procedures under general anesthesia. The final study was conducted under regional anesthesia. All of the studies performed a standard preoperative BG assessment; however, the remaining intervals of assessment vary widely from study to study. Another limitation for comparison is related to every study having a different value for what BG change is considered to be significant, ranging from 23mg/dl to 45mg/dl. One study in particular had limited findings due to the use of insulin for any BG > 215mg/dl. Also, one study infused a glucose (5%) and electrolyte infusion to all patients at a rate of 80ml/hr. Lastly, none of the studies examined the incidence of complications related to hyperglycemia.

The findings of this systematic review determined that in the adult diabetic surgical population, dexamethasone 8mg IV was associated with an increase in perioperative BG levels. Although, the increase may not have been statistically significant.

Next, the recommendations and implications for advanced nursing practice will be presented.

**Recommendations and Implications for Advanced Nursing Practice**

Diabetic surgical patients present with a variety of dynamic alterations in physiologic response. Recognition and identification of patients with diabetes, particularly those with impaired glucose tolerance and associated pathologies, becomes imperative. This is especially important as over a third of diabetic patients are undiagnosed, or untreated, when presenting for surgery (Vinik et al., 2003). Anticipation of complications related to end-organ disease in the diabetic surgical patient is crucial for the anesthesia provider when constructing the anesthetic plan. Perioperatively, diabetic patients have a two- to threefold increase in morbidity and mortality related to cardiovascular complications. Much of the organ dysfunction can be related to diabetic autonomic neuropathy produced from diffuse damage to peripheral nerves and small vessels. The widespread distribution of the autonomic nervous system (ANS) renders all organs susceptible to dysfunction (Vinik et al., 2003).

Diabetic autonomic neuropathy first manifests in longer nerves. The Vagus nerve is responsible for ~75% of all parasympathetic activity and is the longest nerve, resulting in early dysfunction. Gastric emptying (gastroparesis) principally relies on vagal nerve function. Approximately 50% of patients with chronic diabetes suffer from gastroparesis, increasing their perioperative risk for nausea and vomiting and also aspiration. Preoperative testing must be focused on identification and treating coexisting conditions to ensure patients are optimized in order to reduce the incidence of perioperative complications (Kadoi, 2010).

Due to increased gastric dysfunction, diabetic patients require careful consideration when planning prophylaxis treatment of postoperative nausea and vomiting

(PONV). Dexamethasone is one of the most common prophylactic medications used in the perioperative period for its antiemetic and analgesic effects. The use of dexamethasone is, however, also associated with impaired wound healing and hyperglycemia, which are complications diabetic patients are already predisposed to (Godshaw et al., 2019). A retrospective chart review completed by Godshaw et al. (2019) examined the use of dexamethasone in prevention of PONV and for analgesia in 2,317 patients undergoing primary total hip or knee arthroplasty. The primary outcome evaluated was the incidence of prosthetic joint infection (PJI). Participants were principally divided into dexamethasone group and no dexamethasone group, and then further subdivided into diabetic and nondiabetic cohorts. There were 428 diabetic patients in the dexamethasone group that received either 6mg or 12mg of IV dexamethasone preoperatively and 229 diabetics that were allocated in the no dexamethasone group. A total of 25 (1.08%) PJIs were reported in the study, with diabetics having a significantly higher incidence of PJI in comparison to nondiabetics (2.59% versus 0.48%, $p < 0.001$). There was no significant interaction between the use of dexamethasone and diabetic status ($p = 0.646$). This suggests that the use of dexamethasone was not a contributory factor in the development of PJI (Godshaw et al., 2019).

This systematic review concluded that dexamethasone was associated with an increase in perioperative blood glucose levels, although a significant increase was not found among all studies. The Society for Ambulatory Anesthesia suggests that for the well-controlled diabetic patient, intraoperative BG levels should be maintained <180 mg/dL (10.0 mmol/L) and poorly controlled diabetics should be maintained around their

preoperative baseline (Joshi et al., 2010). Chronic elevation of blood glucose levels in the diabetic patient should not be treated perioperatively with insulin due to altered counterregulatory responses leading to hypoglycemic symptoms at decreased and/or "normal" levels (Joshi et al., 2010). Vigilance from the anesthesia provider is required in monitoring intraoperative blood glucose levels due to the detrimental effects of both hypo and hyperglycemia.

The management of the diabetic patient during the perioperative period must be tailored to each individual patient. Hyperglycemia and hypoglycemia are associated with increased morbidity and mortality; therefore, it is up to the anesthesia provider to monitor the patient's blood glucose levels throughout the perioperative period in order to deter these complications (Joshi et al., 2010). Despite widely available point of care blood glucose testing and the known incidence of hyperglycemia associated with dexamethasone use; blood glucose levels may not be commonly monitored after anesthesia. A retrospective study completed by Sudlow et al. (2017) examined the incidence of subsequent measurement of blood glucose levels for 24-hours following anesthesia. Out of 355 patients eligible for chart review, 243 (66%) received dexamethasone at a median dose of 6.7mg. Only 16 patients (4.5%) received subsequent blood glucose assessments. From these 16 patients, eight patients (50%) were diabetic and only two patients received additional blood glucose assessments within the 24-hour time period. Three patients with diabetes developed wound infections with noted blood glucose levels ranging from 216 – 486 mg/dl within 24 hours postoperatively (Sudlow et al., 2017).

Individualization of the anesthetic plan is essential; the anesthesia provider must assess and evaluate the patient to allow for anticipation of potential complications. Although individualization is key, standardization of protocols, specifically, blood glucose assessments during the perioperative period allow for safer management of the diabetic patient. This study concluded that dexamethasone does increase blood glucose levels after administration, therefore benefit versus harm must be weighed for each patient. When choosing to use dexamethasone in the adult diabetic surgical population for prevention of PONV, the risk of an increased stress response, possibility of impaired wound healing, and increased risk of infection must be evaluated against the benefit of its antiemetic and analgesic properties. Further research is needed to deduce whether a single dose of dexamethasone for prevention of PONV has any correlation with adverse outcomes such as surgical site infection or impaired wound healing. Communication with the interdisciplinary teams caring for the patient is also important. A handoff report to the PACU nurse, Advanced Practice Registered Nurse (APRN) and/or physician, summarizing your anesthetic plan and possible future implications is necessary to monitor for adverse outcomes. Continued education amongst providers and care givers is necessary to promote the best possible outcomes while minimizing complications.

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# Appendix A

Table A-1

*Study Specific Data*

| Study 1: Nazar, C. E., Lacassie, H. J., López, R. A., & Muñoz, H. R. (2009). Dexamethasone for postoperative nausea and vomiting prophylaxis: Effect on glycaemia in obese patients with impaired glucose tolerance. *European Journal of Anaesthesiology, 26,* 318-321. | | | | | |
|---|---|---|---|---|---|
| AIM/PURPOSE | DESIGN | SITE | SAMPLE | METHODS | PROCEDURES |
| Investigate the effect of administering dexamethasone in the perioperative period on patients with poor glycemic control undergoing laparoscopic Roux-en-Y gastric bypass surgery. | Single-center, prospective, double-blind randomized trial.<br><br>Group 1 – dexamethasone<br><br>Group 2 – control group | Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile. | 30 obese patients (BMI >35kg/$m^2$) with impaired glucose tolerance were randomly divided into two groups.<br><br>Group 1 – (n=15) dexamethasone<br><br>Group 2 – (n=15) control group<br><br>All patients underwent laparoscopic Roux-en-Y gastric bypass surgery. | Baseline blood glucose (BG) level was obtained in pre-op with IV placement. BG levels reassessed every 2 hours after surgical start for 12 hours. A difference of 2.5 mmol $liter^{-1}$ (45 mg/dl) in peak glucose values between groups is considered statistically significant. All patients received a postoperative infusion of glucose (5%) and electrolytes at a rate of 80ml/hr. The BG levels were not corrected during the study.<br><br>Group 1 –dexamethasone 8mg IV immediately after induction of anesthesia.<br><br>Group 2 – 2ml isotonic saline IV immediately after induction of anesthesia. | Standardized surgical technique per institution protocol.<br><br>Total gastroplasty with gastric pouch (30ml) with 150cm exclusion of small intestine and gastrojejunal anastomosis. |

## Appendix A

Table A-2

*Study Specific Data*

| Study 2: Abdelmalak, B. B., Bonilla, A. M., Yang, D., Chowdary, H. T., Gottlieb, A., Lyden, S. P., & Sessler, D. I. (2013). The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. *Anesthesia & Analgesia, 115*(5) 1116-1122 | | | | | |
|---|---|---|---|---|---|
| AIM/PURPOSE | DESIGN | SITE | SAMPLE | METHODS | PROCEDURES |
| Investigate the change of blood glucose from preoperative to maximal intraoperative after administration of dexamethasone 8mg IV to diabetic and nondiabetic patients undergoing noncardiac surgery under general anesthesia. | Single-center, placebo-controlled, randomized to dexamethasone or placebo, stratified by the presence or absence of diabetes.<br><br>Group 1 – DM1 diabetics receiving dexamethasone<br><br>Group 2 – DM2 diabetics receiving placebo<br><br>Group 3 – ND1 nondiabetics receiving dexamethasone<br><br>Group 4 – ND2 nondiabetics receiving placebo | Cleveland Clinic, Cleveland, Ohio, United States of America. | 185 patients ≥40 years of age undergoing major noncardiac surgery. Restricted to all patients in the conventional glucose group.<br><br>DM1 – (n=21) diabetics receiving dexamethasone<br><br>DM2 – (n=28) diabetics receiving placebo<br><br>ND1 –(n=69) nondiabetics | Fasting BG level was obtained preoperatively. A mean group difference of ≥ 28 mg/dl signified clinical relevance.<br><br>Insulin was given when BG levels were >215 mg/dl to maintain target range of 180 to 200 mg/dl<br><br>Sample 0: preoperative; BG was assessed at least hourly when stable* and every | All patients received a general anesthetic with sevoflurane in air and oxygen for a noncardiac surgery in addition to a standardized infusion of IV fentanyl. |

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| | Patients were part of a larger underlying study in which they were randomized to either tight glucose control with a target plasma concentration of 80 to 110 mg/dl or conventional glucose control of 180 to 200 mg/dl, regardless of diabetic status: The Dexamethasone, Light Anesthesia and Tight Glucose Control [DeLiT] Trial. | | receiving dexamethasone<br><br>ND2 –(n=67) nondiabetics receiving placebo | 30 minutes after intervention**<br><br>DM1 – dexamethasone 8mg IV 1 to 2 hours pre-incision<br><br>DM2–placebo<br><br>ND1 – dexamethasone 8mg IV 1 to 2 hours pre-incision<br><br>ND2 – placebo | |

*Note:* (*) Stable BG – no interventions such as insulin bolus or adjustment of insulin infusion, with two consecutively similar BG readings. (**) Interventions included insulin boluses or adjustment of insulin infusion rate. DM – diabetic group, ND – nondiabetic group.

# Appendix A

Table A-3

*Study Specific Data*

| Study 3: Tien, M., Gan, T. J., Dhakal, I., White, W. D., Olufolabi, A. J., Fink, R., Mishriky, B. M., Lacassie, H. J., & Habib, A. S. (2016). The effect of anti-emetic doses of dexamethasone on postoperative blood glucose levels in non-diabetic and diabetic patients: A prospective randomized controlled study. *Anaesthesia, 71,* 1037-1043. | | | | | |
|---|---|---|---|---|---|
| AIM/PURPOSE | DESIGN | SITE | SAMPLE | METHOD | PROCEDURE |
| Investigate the effect of prophylactic administration of dexamethasone or ondansetron for prevention of postoperative nausea and vomiting and the effects on blood glucose levels in non-diabetic and type-2 diabetic surgical patients. | Single-center, prospective, randomized trial.<br><br>Group 1 – non-diabetics receiving dexamethasone<br><br>Group 2 – non-diabetics receiving ondansetron<br><br>Group 3 –type 2 diabetics receiving dexamethasone<br><br>Group 4 – type 2 diabetics receiving ondansetron | Hospital peri-operative unit, United States | 85 adult English-speaking patients scheduled for a general anesthetic elective surgery anticipated to last >1 hour and expected to be admitted to the hospital for at least 24 hours<br><br>Group 1 – (n=20) non-diabetics receiving dexamethasone<br><br>Group 2 – (n=21) non-diabetics | Baseline blood sample was obtained in pre-op and sent to the central laboratory for measurement. A mean increase in BG levels by 1.7 mmol liter$^{-1}$ (30.6 mg/dl) is to be considered significant. Additional samples were sent at set time intervals: 2 hours, 4 hours, and 24 hours.<br><br>Group 1 – dexamethasone 8mg IV at induction of anesthesia. | A variety of surgical procedures were preformed and classified into the following groups: open gynaecological, laparoscopic gynaecological, open abdominal, laparoscopic abdominal, or other. |

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| | | | receiving ondansetron<br><br>Group 3 – (n= 20) type 2 diabetics receiving dexamethasone<br><br>Group 4 – (n= 24) type 2 diabetics receiving ondansetron | Group 2 – ondansetron 4mg IV towards end of procedure<br><br>Group 3 – dexamethasone 8mg IV at induction of anesthesia.<br><br>Group 4 – ondansetron 4mg IV towards end of procedure | |

## Appendix A

Table A-4

*Study Specific Data*

| Study 4: Purushothaman, A. M., Pujari, V. S., Kadirehally, N. B., Bevinaguddaiah, Y., & Reddy, P. R. (2018). A prospective randomized study on the impact of low-dose dexamethasone on perioperative blood glucose concentrations in diabetics and nondiabetics. *Saudi Journal of Anesthesia, 12*(2), 198-203. | | | | | |
|---|---|---|---|---|---|
| AIM/PURPOSE | DESIGN | SITE | SAMPLE | METHODS | PROCEDURES |
| Investigate the effect of administering two low doses (4mg or 8mg) of dexamethasone on BG levels of diabetic and nondiabetic patients receiving spinal anesthesia for elective surgeries | Single-center, prospective, placebo-controlled randomized trial.<br><br>Group 1 (DM0) – diabetic control group<br><br>Group 2 (DM4) – diabetic group<br><br>Group 3 (DM8) – diabetic group | Department of Anaesthesiology, Ramaiah Medical College and Hospital, Bengaluru, Karnataka, India. | 180 elective surgical patients undergoing spinal anesthesia aged 18 – 70 years.<br><br>DM0 – (n=30) diabetic control group<br><br>DM4 – (n=30) diabetic group receiving dexamethasone 4mg IV<br><br>DM8 – (n=30) diabetic group receiving | Baseline capillary BG level was obtained immediately prior to administration of dexamethasone or control and reassessed every hour for 7 hours. A mean BG change of 23 mg/dl is to be considered clinically significant. The test drugs were reconstituted to a volume of 5mls and given immediately prior to delivery of spinal anesthetic.<br><br>DM0 – 5ml normal saline<br><br>DM4 – dexamethasone 4mg IV | A standardized spinal anesthetic was followed using aseptic technique - 25-gauge Quincke needle delivering 0.5% hyperbaric bupivacaine 15mg and buprenorphine 60 mcg at either L2-L3 or L3-L4 midline approach.<br><br>A total of 133 general surgeries, 24 gynecologic, and 43 orthopedic/plastic and other surgeries were included. |

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|---|---|---|---|---|---|
| | Group 4 (ND0) – nondiabetic control group<br><br>Group 5 (ND4) – nondiabetic group<br><br>Group 6 (ND8) – nondiabetic group | | dexamethasone 8mg IV<br><br>ND0 – (n=30) nondiabetic control group<br><br>ND4 – (n=30) nondiabetic group receiving dexamethasone 4mg IV<br><br>ND8 – (n=30) nondiabetic group receiving dexamethasone 8mg IV | DM8 – dexamethasone 8mg IV<br>ND0 – 5ml normal saline<br><br>ND4 – dexamethasone 4mg IV<br><br>ND8 – dexamethasone 8mg IV | |

*Note:* DM – diabetic group, ND – nondiabetic group

# Appendix B

Table B-1

*Outcome Data Collection*

| Study 1: Nazar, C. E., Lacassie, H. J., López, R. A., & Muñoz, H. R. (2009). Dexamethasone for postoperative nausea and vomiting prophylaxis: Effect on glycaemia in obese patients with impaired glucose tolerance. *European Journal of Anaesthesiology, 26,* 318-321. | | | | |
|---|---|---|---|---|
| Time after start of surgery (hours) | Group 1 dexamethasone (n=15) BG (mg/dl) • | Group 2 control (n=15) BG (mg/dl) • | *p*-value | Significance |
| Baseline | 90.0 ± 10.8 | 88.2 ± 9.0 | | All BG samples measured after the beginning of surgery were higher compared to baseline in both groups. Group 1, the dexamethasone group, exhibited higher BG levels from the 6th to the 12th hour after anesthesia compared to the control group. |
| 2 | 122.4 ± 28.8 | 129.6 ± 32.4 | * | |
| 4 | 147.6 ± 25.2 | 135.0 ± 18.0 | * | |
| 6 | 158.4 ± 18.0 | 126.0 ± 18.0 | * † | |
| 8 | 176.4 ± 25.2 | 129.6 ± 36.0 | * † | |
| 10 | 180.0 ± 32.4 | 127.8 ± 34.2 | * † | |
| 12 | 162.0 ± 21.6 | 122.4 ± 28.8 | * † | |
| Maximum BG levels | 187.2 ± 28.8 | 158.4 ± 30.6 | < 0.05 | |

*Note.* (•) BG concentration converted to mg/dl with formula: mg/dl = 18 x mmol liter$^{-1}$. (*) A *p*-value of less than 0.05 compared with baseline with the paired Student's *t*-test. (†) A *p*-value of less than 0.05 between the groups with the unpaired Student's *t*-test.

# Appendix B

Table B-2.1

*Outcome Data Collection*

| Study 2: Abdelmalak, B. B., Bonilla, A. M., Yang, D., Chowdary, H. T., Gottlieb, A., Lyden, S. P., & Sessler, D. I. (2013). The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. *Anesthesia & Analgesia, 115*(5) 1116-1122 | | | | | |
|---|---|---|---|---|---|
| BG sample times | Group DM1 dexamethasone 8mg IV (n= 21) BG (mg/dl) | Group DM2 control (n=28) BG (mg/dl) | Mean Difference (97.5% CI)[a] | *p*-value[a] | Significance |
| Diabetic baseline BG | 143.0 ± 53.0 | | | | Mean maximal BG change did not change significantly between the DM and ND patients ($p$=0.39). Dexamethasone increased the mean maximal BG, change compared to control, in ND patients ($p$=0.0012); no hyperglycemic response to dexamethasone was seen in DM patients ($p$=0.99). |
| Intraoperative maximal BG change | 63.0 ± 66.0 | 63.0 ± 72.0 | 0 (-33, 33) | 0.99 | |
| Diabetic mean maximal BG change | 63.0 ± 69 | | | 0.39 | |
| Diabetics given insulin treatment intraoperatively | 19 of 49 (39%) | | | <0.001 | |

*Note.* DM – diabetic group, ND – nondiabetic group, CI – confidence interval. ([a]) Linear regression model incorporating factors for placebo vs dexamethasone and DM vs ND; the interaction between DM and dexamethasone was significant ($p$= 0.094, less than criterion of $p$< 0.10); Bonferroni correction was used for two comparisons ($\alpha = 0.05/2 = 0.025$).

# Appendix B

Table B-2.2

*Outcome Data Collection*

| Study 2: Abdelmalak, B. B., Bonilla, A. M., Yang, D., Chowdary, H. T., Gottlieb, A., Lyden, S. P., & Sessler, D. I. (2013). The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. *Anesthesia & Analgesia, 115*(5) 1116-1122 | | | | | |
|---|---|---|---|---|---|
| BG sample times | Group ND1 dexamethasone 8mg IV (n=69) BG (mg/dl) | Group ND2 control (n=67) BG (mg/dl) | Mean Difference (97.5% CI)[a] | *p*-value[a] | Significance |
| Nondiabetic baseline BG | 96.0 ± 19.0 | | | | Mean maximal BG change did not change significantly between the DM and ND patients ($p$=0.39). Dexamethasone increased the mean maximal BG, change compared to control in ND patients ($p$=0.0012); no hyperglycemic response to dexamethasone was seen in DM patients ($p$=0.99). |
| Intraoperative maximal BG change | 86.0 ± 41.0 | 58.0 ± 45.0 | 29 (9, 49) | 0.0012 | |
| Nondiabetic mean maximal BG change | 72.0 ± 54 | | | 0.39 | |
| Nondiabetics given insulin treatment intraoperatively | 8 of 136 (6%) | | | <0.001 | |

*Note:* DM – diabetic group, ND – nondiabetic group, CI – confidence interval. ([a]) Linear regression model incorporating factors for placebo vs dexamethasone and DM vs ND; the interaction between DM and dexamethasone was significant ($p$= 0.094, less than criterion of $p$< 0.10); Bonferroni correction was used for two comparisons ($\alpha = 0.05/2 = 0.025$).

## Appendix B

Table B-3

*Outcome Data Collection*

| Study 3: Tien, M., Gan, T. J., Dhakal, I., White, W. D., Olufolabi, A. J., Fink, R., Mishriky, B. M., Lacassie, H. J., & Habib, A. S. (2016). The effect of anti-emetic doses of dexamethasone on postoperative blood glucose levels in non-diabetic and diabetic patients: A prospective randomized controlled study. *Anaesthesia, 71,* 1037-1043. | | | | | | | |
|---|---|---|---|---|---|---|---|
| BG sample times (hours) | Group 1 non-diabetics dexamethasone (n=20) BG (mg/dl) • | Group 2 non-diabetics ondansetron (n=21) BG (mg/dl) • | *p*-value | Group 3 type 2 diabetics dexamethasone (n=20) BG (mg/dl) • | Group 4 type 2 diabetics ondansetron (n=24) BG (mg/dl) • | *p*-value | Significance |
| 0 h | 95.4 ± 16.2 | 91.8 ± 14.4 | 0.62 | 124.2 ± 28.8 | 129.6 ± 34.2 | 0.59 | In non-diabetic patients, the maximum BG was higher in those who received dexamethasone compared to those who received ondansetron ($p = 0.04$); the same conclusion was exhibited with type 2 diabetic patients who received dexamethasone compared to those who received ondansetron ($p < 0.01$) |
| 2 h | 115.2 ± 18.0 | 118.8 ± 23.4 | 0.65 | 169.2 ± 50.4 | 145.8 ± 39.6 | 0.10 | |
| 4 h | 153.0 ± 28.8 | 131.4 ± 28.8 | 0.02 | 187.2 ± 54.0 | 154.8 ± 37.8 | 0.08 | |
| 24 h | 126.0 ± 45.0 | 1170 ± 18.0 | 0.99 | 176.4 ± 45.0 | 149.4 ± 41.4 | 0.05 | |
| Mean Peak BG | 163.8 ± 39.6 | 140.4 ± 25.2 | 0.04 | 252.0 ± 45.0 | 192.6 ± 43.2 | <0.01 | |
| Maximum 4-h BG change | 57.6 ± 30.6 | 41.4 ± 30.6 | 0.10 | 66.6 ± 48.6 | 28.8 ± 37.8 | <0.01 | |
| Maximum 24-h BG change | 68.4 ± 43.2 | 48.6 ± 30.6 | 0.09 | 126.0 ± 37.8 | 63.0 ± 39.6 | <0.01 | |
| Maximum 24-h BG >180 | 6 (30%) | 2 (10%) | 0.13 | 19 (95%) | 12 (50%) | <0.01 | |

*Note.* (•) BG concentration converted to mg/dl with formula: mg/dl = 18 x mmol liter$^{-1}$.

# Appendix B

Table B-4.1

*Outcome Data Collection*

| Study 4: Purushothaman, A. M., Pujari, V. S., Kadirehally, N. B., Bevinaguddaiah, Y., & Reddy, P. R. (2018). A prospective randomized study on the impact of low-dose dexamethasone on perioperative blood glucose concentrations in diabetics and nondiabetics. *Saudi Journal of Anesthesia, 12*(2), 198-203. | | | | | |
|---|---|---|---|---|---|
| BG sample times | **Group 1 –** DM0(n=30) BG (mg/dl) | **Group 2 –** DM4 (n=30) BG (mg/dl) | **Group 3 –** DM8 (n=30) BG (mg/dl) | *p*-value | Significance |
| T0 | 134.4 ± 22.8 | 125.6 ± 21.0 | 125.8 ± 22.6 | 0.219 | There was a rise in BG levels in both diabetic and nondiabetic groups who received dexamethasone. However, this rise was not clinically significant with a range of 10-15 mg/dl from baseline. BG levels peaked at T4 in the DM4 group, which was a statistically significant increase from baseline. BG levels in the DM8 group peaked at T5. |
| T1 | 139.3 ± 24.5 | 137.7 ± 20.0 | 135.6 ± 26.1 | 0.835 | |
| T2 | 141.2 ± 25.4 | 149.3 ± 20.6 | 143.3 ± 28.0 | 0.426 | |
| T3 | 138.5 ± 26.0 | 161.3 ± 20.5 | 154.2 ± 34.2 | $0.006^{*,\dagger,\ddagger}$ | |
| T4 | 147.3 ± 23.6 | 169.3 ± 21.8 | 166.8 ± 25.9 | $<0.001^{*,\dagger,\ddagger}$ | |
| T5 | 144.4 ± 22.9 | 165.0 ± 21.4 | 167.5 ± 18.6 | $<0.001^{*,\dagger,\ddagger}$ | |
| T6 | 146.9 ± 20.8 | 158.0 ± 25.4 | 160.2 ± 16.0 | $<0.037^{*,\dagger,\ddagger}$ | |
| T8 | 144.5 ± 20.6 | 151.2 ± 20.8 | 149.1 ± 17.0 | 0.401 | |
| Mean Peak BG | 148.0 ± 17.2 | 169.0 ± 17.3 | 168.0 ± 22.4 | | |

*Note.* (*) Indicates *p*-value < 0.05 significant between the three groups by analysis of variance. Post hoc analysis between the groups was done. (†) Indicates *p*-value < 0.05 significant between DM0 and DM4. (‡) Indicates *p*-value < 0.05 significant between DM0 and DM8. T0 (baseline), T1 (60), T2 (120), T3 (180), T4 (240), T5 (300), T6 (360), and T8 (480) minutes after test drug administration. DM: Diabetes group. DM0: control group, DM4: 4mg dexamethasone IV, DM8: 8mg dexamethasone IV.

## Appendix B

Table B-4.2

*Outcome Data Collection*

| Study 4: Purushothaman, A. M., Pujari, V. S., Kadirehally, N. B., Bevinaguddaiah, Y., & Reddy, P. R. (2018). A prospective randomized study on the impact of low-dose dexamethasone on perioperative blood glucose concentrations in diabetics and nondiabetics. *Saudi Journal of Anesthesia, 12*(2), 198-203. | | | | | |
|---|---|---|---|---|---|
| BG sample times | **Group 4 –** ND0 (n=30) BG Concentration (md/dl) | **Group 5 –** ND4 (n=30) BG Concentration (mg/dl) | **Group 6 –** ND8 (n=30) BG Concentration (mg/dl) | *p*-value | Significance |
| T0 | 96.3 ± 11.3 | 93.3 ± 11.6 | 95.5 ± 15.5 | 0.654 | There was a rise in BG levels in both diabetic and nondiabetic groups who received dexamethasone. However, this rise was not clinically significant with a range of 10-15 mg/dl from baseline. BG levels peaked in the ND4 and ND8 groups at T5 and T6, respectively. At T8, in comparison with the DM8 group, the ND8 group had a statistically significant increase in BG levels. |
| T1 | 99.7 ± 12.3 | 98.4 ± 14.8 | 98.5 ± 13.8 | 0.918 | |
| T2 | 102.1 ± 13.4 | 104.9 ± 18.9 | 104.8 ± 15.3 | 0.739 | |
| T3 | 104.9 ± 15.1 | 114.9 ± 19.3 | 116.9 ± 21.2 | 0.034$^{*,‡}$ | |
| T4 | 100.9 ± 23.7 | 126.6 ± 23.3 | 129.4 ± 25.3 | <0.001$^{*,†,‡}$ | |
| T5 | 103.1 ± 24.5 | 133.1 ± 26.1 | 137.8 ± 23.8 | <0.001$^{*,†,‡}$ | |
| T6 | 103.7 ± 15.3 | 124.3 ± 24.5 | 139.9 ± 27.9 | <0.001$^{*,†,‡,§}$ | |
| T8 | 100.3 ± 15.0 | 114.6 ± 21.3 | 131.1 ± 28.1 | <0.001$^{*,†,‡,§}$ | |
| Mean Peak BG | 105.0 ± 23.6 | 133.0 ± 20.4 | 140.0 ± 23.2 | | |

*Note.* (*) Indicates *p*-value < 0.05 significant between the three groups by analysis of variance. Post hocanalysis between the groups was done. (†) Indicates *p*-value < 0.05 significant between ND0 and ND4. (‡) Indicated *p*-value < 0.05 significant between ND0 and ND8. (§) Indicates *p*-value < 0.05 significant between ND4 and ND8. T0 (baseline), T1 (60), T2 (120), T3 (180), T4 (240), T5 (300), T6 (360), and T8 (480) minutes after test drug administration. ND: Nondiabetic group. ND0: control group, ND4: 4mg dexamethasone IV, ND8: 8mg dexamethasone IV.

## Appendix C

Table C-1

| Study 1: Nazar, C. E., Lacassie, H. J., López, R. A., & Muñoz, H. R. (2009). Dexamethasone for postoperative nausea and vomiting prophylaxis: Effect on glycaemia in obese patients with impaired glucose tolerance. *European Journal of Anaesthesiology, 26,* 318-321. | | | | |
|---|---|---|---|---|
| **A)** | **Are the results of the trial valid?** | **Yes** | **Can't tell** | **No** |
| 1. | Did the trial address a clearly focused issue? | X | | |
| 2. | Was the assignment of patients to treatments randomized? | X | | |
| 3. | Were all of the patients who entered the trial properly accounted for at its conclusion? | X | | |
| 4. | Were patients, health workers, and study personnel "bind" to treatment? | X | | |
| 5. | Were the groups similar at the start of the trial? | X | | |
| 6. | Aside from the experimental intervention, were the groups treated equally? | X | | |
| **B)** | **What are the results?** | | | |
| 7. | How large was the treatment effect? | All BG samples measured after the beginning of surgery were higher compared to baseline in both groups. | | |
| 8. | How precise was the estimate of the treatment effect? | Group 1, the dexamethasone group, exhibited higher BG levels from the 6$^{th}$ to the 12$^{th}$ hour after anesthesia compared to the control group. | | |
| **C)** | **Will the results help locally?** | **Yes** | **Can't tell** | **No** |
| 9. | Can the results be applied in your context? | X | | |
| 10. | Were all clinically important outcomes considered? | | X* | |
| 11. | Are the benefits worth the harms and costs? | | X* | |

*Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*

*Note.* (*) The study did not examine differences or complications in outcomes between the two groups related to hyperglycemia, unable to determine.

## Appendix C

Table C-2

*Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*

| Study 2: Abdelmalak, B. B., Bonilla, A. M., Yang, D., Chowdary, H. T., Gottlieb, A., Lyden, S. P., & Sessler, D. I. (2013). The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. *Anesthesia & Analgesia, 115*(5) 1116-1122 | | | |
|---|---|---|---|
| **A) Are the results of the trial valid?** | **Yes** | **Can't tell** | **No** |
| 1. Did the trial address a clearly focused issue? | X | | |
| 2. Was the assignment of patients to treatments randomized? | X | | |
| 3. Were all of the patients who entered the trial properly accounted for at its conclusion? | X | | |
| 4. Were patients, health workers, and study personnel "bind" to treatment? | X | | |
| 5. Were the groups similar at the start of the trial? | | | X[†] |
| 6. Aside from the experimental intervention, were the groups treated equally? | | | X[‡] |
| **B) What are the results?** | | | |
| 7. How large was the treatment effect? | Mean maximal BG change did not change significantly between the DM and ND patients ($p$=0.39). | | |
| 8. How precise was the estimate of the treatment effect? | Dexamethasone increased the mean maximal BG, change compared to control, in ND patients ($p$=0.0012); no hyperglycemic response to dexamethasone was seen in DM patients ($p$=0.99). | | |
| **C) Will the results help locally?** | **Yes** | **Can't tell** | **No** |
| 9. Can the results be applied in your context? | X | | |
| 10. Were all clinically important outcomes considered? | | X* | |
| 11. Are the benefits worth the harms and costs? | | X* | |

*Note.* (†) Patients selected for the study were diabetic and non-diabetic, of varying age, and received various types of surgery. (‡) Patients received insulin for BG levels > 215 mg/dl to maintain BG in the target range 180 to 200 mg/dl (*) The study did not examine differences or complications in outcomes between the two groups related to hyperglycemia, unable to determine.

## Appendix C

Table C-3

*Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*

| Study 3: Tien, M., Gan, T. J., Dhakal, I., White, W. D., Olufolabi, A. J., Fink, R., Mishriky, B. M., Lacassie, H. J., & Habib, A. S. (2016). The effect of anti-emetic doses of dexamethasone on postoperative blood glucose levels in non-diabetic and diabetic patients: A prospective randomized controlled study. *Anaesthesia, 71,* 1037-1043. | | | |
|---|---|---|---|
| **A) Are the results of the trial valid?** | **Yes** | **Can't tell** | **No** |
| 1. Did the trial address a clearly focused issue? | X | | |
| 2. Was the assignment of patients to treatments randomized? | X | | |
| 3. Were all of the patients who entered the trial properly accounted for at its conclusion? | | | X† |
| 4. Were patients, health workers, and study personnel "bind" to treatment? | X | | |
| 5. Were the groups similar at the start of the trial? | | | X‡ |
| 6. Aside from the experimental intervention, were the groups treated equally? | | | X†† |
| **B) What are the results?** | | | |
| 7. How large was the treatment effect? | Multiple variate analysis illustrated that use of dexamethasone was a significant predictor of maximum postoperative BG increase ($p < 0.01$). | | |
| 8. How precise was the estimate of the treatment effect? | In non-diabetic patients, the maximum BG was higher in those who received dexamethasone compared to those who received ondansetron ($p = 0.04$); the same conclusion was exhibited with type 2 diabetic patients who received dexamethasone compared to those who received ondansetron ($p < 0.01$). | | |
| **C) Will the results help locally?** | **Yes** | **Can't tell** | **No** |
| 9. Can the results be applied in your context? | X | | |
| 10. Were all clinically important outcomes considered? | | X* | |
| 11. Are the benefits worth the harms and costs? | | X* | |

*Note.* (†) Three out of 88 patients were discharged early from the hospital and considered lost to follow-up. (‡) Patients selected for the study were diabetic and non-diabetic, of varying age, and received various types of surgery. (††) Diabetic patients received insulin subcutaneously for BG levels > 200 mg/dl. (*) The study did not examine differences or complications in outcomes between the two groups related to hyperglycemia, unable to determine.

## Appendix C

Table C-4

*Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*

| Study 4: Purushothaman, A. M., Pujari, V. S., Kadirehally, N. B., Bevinaguddaiah, Y., & Reddy, P. R. (2018). A prospective randomized study on the impact of low-dose dexamethasone on perioperative blood glucose concentrations in diabetics and nondiabetics. *Saudi Journal of Anesthesia, 12*(2), 198-203. | | | |
|---|---|---|---|
| **A) Are the results of the trial valid?** | **Yes** | **Can't tell** | **No** |
| 1. Did the trial address a clearly focused issue? | X | | |
| 2. Was the assignment of patients to treatments randomized? | X | | |
| 3. Were all of the patients who entered the trial properly accounted for at its conclusion? | X | | |
| 4. Were patients, health workers, and study personnel "bind" to treatment? | X | | |
| 5. Were the groups similar at the start of the trial? | | | X‡ |
| 6. Aside from the experimental intervention, were the groups treated equally? | X | | |
| **B) What are the results?** | | | |
| 7. How large was the treatment effect? | There was a rise in BG levels in both diabetic and nondiabetic groups who received dexamethasone. However, this rise was not clinically significant with a range of 10-15 mg/dl from baseline. | | |
| 8. How precise was the estimate of the treatment effect? | BG levels peaked at T4 in the DM4 group, which was a statistically significant increase from baseline. BG levels in the DM8 group peaked at T5. BG levels peaked in the ND4 and ND8 groups at T5 and T6, respectively. At T8, in comparison with the DM8 group, the ND8 group had a statistically significant increase in BG levels. | | |
| **C) Will the results help locally?** | **Yes** | **Can't tell** | **No** |
| 9. Can the results be applied in your context? | X | | |
| 10. Were all clinically important outcomes considered? | | X* | |
| 11. Are the benefits worth the harms and costs? | | X* | |

*Note:* (‡) Patients selected for the study were diabetic and non-diabetic, of varying age, and received various types of surgery. (*) The study did not examine differences or complications in outcomes between the two groups related to hyperglycemia, unable to determine.

## Appendix D

*Cross Study Analysis*

| Author, Year | Methods | Overall Outcome | Mean BG 2h | Mean BG 4h | Mean BG 6h | Mean BG 8h | Mean Peak BG |
|---|---|---|---|---|---|---|---|
| Study 1 (Nazar et al., 2009) | Group 1- dexamethasone 8mg IV | All BG samples measured after the beginning of surgery were higher compared to baseline in both groups. Group 1 exhibited higher BG levels from the 6th to the 12th hour after anesthesia compared to the control group. | 122.4 ± 28.8 | 147.6 ± 25.2 | 158.4 ± 18.0 | 176.4 ± 25.2 | 187.2 ± 28.8 |
| | Group 2- control | | 129.6 ± 32.4 | 135.0 ± 18.0 | 126.0 ± 18.0 | 129.6 ± 36.0 | 158.4 ± 30.6 |
| Study 2 (Abdelmalak et al., 2013) | Group 1-DM1 dexamethasone 8mg IV | Mean maximal BG change did not change significantly between the DM and ND patients ($p$=0.39). Dexamethasone increased the mean maximal BG, change compared to control in ND patients ($p$=0.0012); no hyperglycemic response to dexamethasone was seen in DM patients ($p$=0.99). | n/a | n/a | n/a | n/a | 209.0 ± 66.0 |
| | Group 2-DM2 control | | n/a | n/a | n/a | n/a | 209.0 ± 72.0 |
| | Group 3- ND1 dexamethasone 8mg IV | | n/a | n/a | n/a | n/a | 182.0 ± 41.0 |
| | Group 4- ND2 control | | n/a | n/a | n/a | n/a | 154.0 ± 45.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Study 3 (Tien et al., 2016) | Group 1- ND dexamethasone 8mg IV | In non-diabetic patients, the maximum BG was higher in those who received dexamethasone compared to those who received ondansetron ($p = 0.04$); the same conclusion was exhibited with type 2 diabetic patients who received dexamethasone compared to those who received ondansetron ($p < 0.01$) | 115.2 ± 18.0 | 153.0 ± 28.8 | n/a | n/a | 163.8 ± 39.6 |
| | Group 2- ND ondansetron 4mg IV | | 118.8 ± 23.4 | 131.4 ± 28.8 | n/a | n/a | 140.4 ± 25.2 |
| | Group 3- DM dexamethasone 8mg IV | | 169.2 ± 50.4 | 187.2 ± 54.0 | n/a | n/a | 252.0 ± 45.0 |
| | Group 4- DM ondansetron 4mg IV | | 145.8 ± 39.6 | 154.8 ± 37.8 | n/a | n/a | 192.6 ± 43.2 |
| Study 4 (Purushothaman et al., 2018) | Group 1- DM control | There was a rise in BG levels in both diabetic and nondiabetic groups who received dexamethasone. However, this rise was not clinically significant with a range of 10-15 mg/dl from baseline. BG levels peaked at T4 in the DM4 group, which was a statistically significant increase from baseline. BG levels in the DM8 group peaked at T5. BG levels | 141.2 ± 25.2 | 147.3 ± 23.6 | 146.9 ± 20.8 | 144.5 ± 20.6 | 148.0 ± 17.2 |
| | Group 2- DM dexamethasone 4mg IV | | 149.3 ± 20.6 | 169.3 ± 21.8 | 158.0 ± 25.4 | 151.2 ± 20.8 | 169.0 ± 17.3 |
| | Group 3- DM dexamethasone 8mg IV | | 143.3 ± 28.0 | 166.8 ± 26.0 | 160.2 ± 16.0 | 149.1 ± 17.0 | 168.0 ± 22.4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Group 4- ND control | peaked for groups ND4 and ND8 at T5 and T6, respectively. At T8, in comparison with the DM8 group, the ND8 group had a statistically significant increase in BG levels. | 102.1 ± 13.4 | 100.9 ± 23.7 | 103.7 ± 15.3 | 100.3 ± 15.0 | 105.0 ± 23.6 |
| | Group 5- ND dexamethasone 4mg IV | | 104.9 ± 18.9 | 126.6 ± 23.3 | 124.3 ± 24.5 | 114.6 ± 21.3 | 133.0 ± 20.4 |
| | Group 6- ND dexamethasone 8mg IV | | 104.8 ± 15.3 | 129.4 ± 25.3 | 139.9 ± 27.9 | 131.1 ± 28.1 | 140.0 ± 23.2 |

*Note.* DM – diabetic group, ND – nondiabetic group. BG = mg/dl