APPENDICES

APPENDIX A

Sample Corpora for Analysis

Anesthetic implications for cancer chemotherapy

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Cancer is one of the most prevalent disease processes affecting people of all ages. Cancer is the second most common cause of death in the United States, exceeded only by heart disease. Cancer survival is dependent on treatment options that may include surgery, radiation, and chemotherapy. Chemotherapy, or systemic cancer therapy, is designed to promote cell death during different phases of cell growth and division. Unfortunately, chemotherapeutic agents cannot differentiate between malignant and normal cells. Therefore, the toxic effects of chemotherapy are also seen in healthy organs and tissues. In addition, chemotherapeutic agents can interact with other medications.

The effects of chemotherapy may be acute and self-limiting or chronic and present long after treatment has been completed. Patients who have had chemotherapy often undergo surgery that may or may not be related to their cancer. Chemotherapy administration can have a profound influence on anesthetic management. Safe administration of anesthesia includes knowledge of chemotherapeutic agents and their toxic effects. This course discusses the anatomic and physiologic effects of cancer chemotherapeutic agents and how they specifically affect patients receiving anesthesia.

Key words: Anesthesia, cancer, chemotherapy, toxicity.

Objectives

At the completion of this course, the reader should be able to:

1. Describe the classes of chemotherapeutic agents and their mechanisms of action.
2. Understand the importance of the preoperative evaluation as it relates to patients who have received or are receiving chemotherapy.
3. Associate chemotherapeutic agents with their related toxic effects.

4. Differentiate between acute and long-term toxic effects seen with chemotherapeutic agents.

5. Refine the anesthetic management of patients who have received or are receiving chemotherapy.

Introduction

Oncological patients are seen by anesthesia providers at multiple phases of the disease process. Patients who have received chemotherapy may demonstrate clinically relevant physical alterations that can affect perioperative anesthetic management. Alterations may include deviations in bone marrow production and immunity and renal, lung, and cardiac dysfunction. This course discusses the anatomic and physiologic effects of cancer chemotherapeutic agents and how they specifically affect patients receiving anesthesia. Understanding the anesthetic implications of chemotherapeutic agents and their sequelae is essential in providing quality patient care.1

Cancer statistics

The American Cancer Society's annual estimate of new cancer cases in the United States for the year 2007 is 1,444,920. Deaths attributable to cancer will be 559,650, or more than 1,500 people a day. It is the second most common cause of death in the United States, exceeded only by heart disease. When aggregated by age, death due to cancer has surpassed death due to heart disease in people younger than 85 years.2,3

The most commonly diagnosed cancer in men is prostate cancer, and it alone will account for 29% of cancers in men in the coming year. Breast cancer is the most frequently diagnosed cancer in women and will account for 26% of total newly diagnosed cancer cases for women in 2007. Lung cancer continues to be the leading cause of cancer death in men and women.3 Table 1 lists the top 10 diagnosed cancers in men and women along with common chemotherapeutic agents used to treat them.

Chemotherapy

Chemotherapeutic agents act by interfering with the cell cycle at different phases of cell replication. Unfortunately, because of this mode of action, there is no drug that can destroy cancer cells without also damaging normal healthy cells. In contrast with traditional cancer therapy, newer treatments are more cell-specific and less globally cytotoxic but are still associated with the potential for serious side effects.4 Classifications of cytotoxic drugs are determined by their specificity in the cell cycle. Classes include alkylating agents, antimetabolites, antitumor antibiotics, and vinca alkaloids (Table 2). Some drugs are loosely classified as miscellaneous because their mechanism of action is not fully understood or their action does not conform to one of the more specific classifications. 5 Alkylating agents affect DNA, causing cross-linking and abnormal base pairing and resulting in intracellular imbalance and cell death. Antimetabolites or structural analogs interfere with cell replication by substitution of metabolites necessary for cell reproduction. Antitumor antibiotics act by inhibiting DNA and RNA synthesis. Vinca alkaloids are known to interact with the microtubular proteins needed for cell division.5 Toxic effects are related to the type of drug, the cumulative dose, and the dosing schedule.6,7

In preparation for administering anesthesia to a patient receiving or who has received chemotherapy, a comprehensive preoperative history and physical examination are paramount. Full knowledge of all cancer treatment received by the patient, including surgery and radiation, may reveal potential operative complications such as exacerbation of surgical bleeding. 1 Information obtained by anesthesia providers about cancer treatment received by patients should be exhaustive and include type of chemotherapeutic agents, number of treatments, date of last treatment, and total amount of agent received.6 Patients and family members are often unable to provide complete and accurate information pertaining to cancer treatment. Anesthesia providers may need to access other sources, such as charts from prior admissions, to obtain the necessary information.

Central nervous system effects

Central nervous system toxicity resulting in nausea and vomiting consistently ranks among the top 3 reported side effects of chemotherapy. Onset is usually acute, occurring within 12 to 24 hours after treatment. Delayed nausea and vomiting occurs after 24 hours and may last for 6 to 7 days.8 Cisplatin in high doses will cause vomiting within 24 hours of administration in 90% of patients who are not taking prophylactic antiemetics.8 Emetogenicity risk factors for patients receiving chemotherapy are the same as for patients who experience postoperative nausea and vomiting. These factors include young age, female gender, and history of motion sickness.

Vomiting patients are at risk for electrolyte imbalances, dehydration, weight loss, and malnutrition. Patients experiencing nausea alone may have flushing and tachycardia. Prevention of aspiration remains a primary concern to anesthesia providers, and this patient population presents an increased risk. A reliable and valid self-reporting instrument such as the Rhodes Index of Nausea, Vomiting, and Retching may be a valuable assessment tool. This information will provide a view of the patient's personal symptom experience, allowing the anesthesia provider to plan appropriate symptom management.

Other central nervous system effects include seizures, which may occur with busulfan treatment up to 24 hours after the last dose. Numbness and tingling of extremities, loss of deep tendon reflexes, and weakness of distal limb musculature are toxic signs of vincristine therapy.9 Other chemotherapeutic agents associated with neuropathies include cisplatin, taxanes, and oxaliplatin.10 Vinca alkaloids have been the causative agent in vocal cord paralysis and loss of extraocular muscle function. Central nervous system toxic reactions usually disappear after discontinuation or dosage adjustment.9 Agents that may cause central nervous system toxicity are listed in Table 3.

Cardiac effects

Hemodynamic stability is an important aspect of anesthetic management and may be impaired by cardiotoxicity. Cytostatic anthracycline antibiotics are the chemotherapeutic agents most commonly associated with cardiotoxicity.11 Anthracyclines are a subset of the antibiotic

class of chemotherapeutic agents and include daunorubicin, doxorubicin, epirubicin, and idarubicin. Other agents that also induce this phenomenon are listed in Table 4. Because the myocardium consists of cells that have limited regenerative capability, the heart is susceptible to permanent damage.12

The 3 established forms of anthracycline-induced cardiotoxicity are separated into acute, chronic, and late onset. Acute cardiotoxicity pertains to an onset immediately after a single dose or course of therapy and is usually transient. It may involve abnormal electro-cardiographic findings, including ST-T wave changes, QT-interval prolongation, and arrhythmias. Chronic toxic effects occur within 1 year of therapy, with rapid onset and progression. Manifestations include tachycardia, tachypnea, ventricular dilation, exercise intolerance, pulmonary and venous congestion, poor perfusion, and pleural effusion. This toxicity reflects progressive injury and loss of myocytes and will eventually lead to congestive heart failure and decreased left ventricular ejection fraction. Late-onset toxic effects occur several years or decades after therapy cessation. These effects include ventricular dysfunction, conduction disturbances and arrhythmias, and congestive heart failure as a consequence of myocyte damage. Late-onset toxic effects typically occur in patients who received anthracycline therapy as a child or adolescent and can occur even with low doses. Other clinical signs of cardiotoxicity include mild blood pressure changes, thrombosis, myocarditis, pericarditis, myocardial infarction, and cardiomyopathy.13

Risk factors that can increase the incidence of chemotherapy-related cardiotoxicity are history of radiation therapy to the mediastinum or left chest wall, age at treatment (higher incidence in younger patients), preexisting cardiac disease, obesity, and left ventricular ejection fraction of less than 50%.14 These factors and the type of surgery must be considered when evaluating cardiac status before anesthesia. A chest radiograph, a 2-dimensional echocardiogram, an electrocardiogram, and the levels of lactate dehydrogenase and creatine phosphokinase enzymes can be indicative of altered myocardial function. Anesthesia providers must keep in mind that abnormalities in cardiac function can exist even in patients with normal resting cardiac function.11 Patients who have received anthracycline therapy may have an enhanced cardiodepressive effect from anesthesia.11 In a compromised patient, prolonged sympathetic hyperactivity maintains cardiac function and the number of β adrenergic receptors

may be decreased. Therefore, ÃŸ-adrenergic agonists may be ineffective, and a non-adrenergic inotropic agent should be considered. Anesthetics with negative inotropic effects, such as halothane, should be avoided. Chronic sympathetic stimulation maintains cardiac function in compromised patients; therefore, ketamine may depress, rather than enhance, cardiac function.1

Pulmonary effects

When pulmonary toxic effects occur from cytotoxic agents, they involve a combination of direct lung damage and indirect inflammatory processes.15 In general, the adverse respiratory effects from cytotoxic agents are composed of an early inflammatory interstitial pneumonitis, acute noncardiogenic pulmonary edema, bronchospasm, and pleural effusion.11 Some of the signs and symptoms associated with these effects include dyspnea, cough, tachypnea, bibasilar rales, and, occasionally, fever. Pneumonitis occurs gradually in the first few months of treatment but can occur as long as 6 months after treatment.16 Pneumonitis is accompanied by an increase in fibroblast activity. Fibroblast activity is then followed by collagen synthesis and decreased collagen degradation, leading to pulmonary fibrosis.17 There is a wide range of cytotoxic chemotherapy agents that have been implicated in pulmonary fibrosis and are listed in Table 5. Bleomycin is the chemotherapeutic agent most associated with toxicity that can lead to pulmonary fibrosis.11 Fibrosis is accompanied by dyspnea, hacking cough, fatigue, chest discomfort, and rapid weight loss. Up to 25% of patients with previous bleomycin therapy may develop postoperative respiratory insufficiency, necessitating prolonged postoperative intubation.11 Preoperative assessment should include questions that focus on accompanying risk factors that may increase the likelihood of postoperative respiratory insufficiency. Risk factors for pulmonary toxicity from chemotherapeutic agents include age older than 70 years, genetic predisposition, existing pulmonary disease, smoking history, and thoracic radiation therapy. Pulmonary function tests, such as vital capacity and diffusion capacity for carbon monoxide, are commonly monitored to detect chemotherapy-induced pulmonary toxicity.15 Measurement of diffusion capacity of carbon monoxide (>10%-15% from baseline) has been found to be the most sensitive indicator of subclinical pulmonary damage from chemotherapeutics.15 The 2 main concerns for anesthesia providers are the administration of intraoperative oxygen and fluid management.

High oxygen concentrations have been implicated in potentiating lung damage in patients who received bleomycin. Hyperoxia is the delivery of inspired oxygen concentrations equal to or greater than 30%. Previous bleomycin treatment sensitizes the lung to concentrations of oxygen that are not usually damaging.18 Recommendations are to use less than 30% inspired oxygen or the lowest inspiratory oxygen fraction compatible with adequate tissue oxygenation. Arterial blood gases and pulse oximetry can be used to determine adequate oxygenation. In surgical procedures in which inspired oxygen of more than 30% is warranted, more invasive monitoring, such as mixed venous oximetry, may allow anesthetists to minimize oxygen concentrations safely. Treatment with corticosteroids before surgery has shown positive results with improvements in vital capacity and diffusion capacity and no postoperative respiratory complications.17 Equally important as the use of low oxygen concentrations is the careful management of intravenous fluid administration. The restriction of fluids to the minimum necessary to maintain hemodynamic stability and adequate renal output is advised.11 There is a high percentage of subclinical bleomycin-induced pulmonary damage compromising the ability of the lungs to handle large volumes of fluids.11 With proper assessment and management, the probability of postoperative respiratory complications related to prior chemotherapy-induced lung toxicity should be reduced.

Nephrotoxicity

Administration of anticancer chemotherapy can cause drug-induced nephrotoxicity and can lead to acute or chronic renal damage.19 Approximately 20% of cardiac output perfuses the kidneys, exposing these organs extensively to systemic chemotherapeutic agents.20 Mechanisms of renal dysfunction generally include damage to structures of the kidneys necessitating evaluation of glomerular filtration, proximal tubular function, and distal tubular function. Hemolytic uremic syndrome and prerenal perfusion deficits are also observed in patients treated with cancer chemotherapy.20 Patients typically experience nonoliguric renal failure.9 Nephrotoxic cancer chemotherapeutic agents include methotrexate, cisplatin, and ifosfamide (Table 6). Chemotherapy dose-related degrees of nephrotoxicity are experienced with the platinating agents cisplatin and carboplatin. Electrolyte abnormalities subsequent to cisplatin administration occur acutely and may persist for years following cessation of therapy.

Hypomagnesemia occurs more commonly than hypokalemia, other electrolyte abnormalities, or acid-base disorders. Cisplatin administration is also responsible for acute proximal tubular damage followed by a progressive loss of filtration capability. Transient renal dysfunction occurs frequently and irreversible renal dysfunction occurs infrequently following administration of carboplatin.20 Common signs of platinum-induced nephrotoxicity include increased serum creatinine level, uremia, and electrolyte abnormalities.

Estimation of glomerular filtration rate using creatinine clearance is used to assess renal function.20 Maintaining fluid and electrolyte balance and adequate renal perfusion are the critical factors in treating patients at risk for nephrotoxic effects.1 Nonsteroidal anti-inflammatory drugs should be avoided in patients receiving nephrotoxic chemotherapy because they may precipitate acute renal failure.11 Dosages of drugs that undergo renal clearance, such as pancuronium, should be decreased. Isoflurane and desflurane are the volatile agents of choice due to the association of sevoflurane with nephrotoxic compound A.

Hepatic implications

Hepatic dysfunctions, such as cirrhosis and coagulation disorders, are frequently reversible effects of cancer chemotherapy. Methotrexate may induce the development of hepatic cirrhosis and fibrosis. Although rare, flutamide causes severe hepatotoxicity with associated jaundice and dark urine.9 Other hepatotoxic chemotherapeutic agents are listed in Table 6. Hepatocellular damage may be exacerbated in patients undergoing anesthesia.1 Hepatic metabolism must be considered, and isoflurane is the preferred volatile agent.6 Halothane has been implicated in hepatotoxicity and should be avoided. Vecuronium and rocuronium should be used judiciously and closely monitored. Liver function tests may be useful in monitoring patients who have received a hepatotoxic chemotherapy regimen.

Gastrointestinal effects

Effects of chemotherapy are manifested in the rapidly dividing cells of the entire gastrointestinal tract, and the potential for substantial mucosal tissue injury exists throughout the length of the tract.21 Gastrointestinal disorders may include oral mucositis or diarrhea and are limited to patients actively receiving chemotherapy. Chemotherapeutic regimens containing

fluorouracil and irinotecan have been associated with a significantly higher risk of chemotherapy-induced diarrhea (see Table 6).22 Perioperative evaluations of urine osmolarity, specific gravity, and serum electrolytes will provide information for managing fluid and electrolyte losses associated with diarrhea.

Oral mucositis is defined as oral mucosal change secondary to cancer therapy. Ulceration eventually occurs in concurrence with severe, debilitating oral pain, usually requiring narcotic analgesia. Signs may include mucosal whitening followed by erythema and bleeding. Healing will occur within 2 to 3 weeks after chemotherapy is ended. Oral inflammation and ulceration may present concerns to anesthetists when attempting endotracheal intubation. Patients are at a greatly increased risk for the spread of oral organisms, through oral ulceration, into the systemic circulation. Friable mucosa may be subject to bleeding. Pain may limit the patients' intake, culminating in dehydration and nutritional deficits. Occurrence is 1% to 10% and is seen in anthracycline-, taxane-, and platinum-based regimens. Incidence increases when treatments are combined with fluorouracil.23

Myelosuppression

Myelosuppression is the toxic effect most frequently encountered with chemotherapy. Tissues in the body that divide rapidly are the most susceptible to the toxic side effects including hematopoietic cells.24 Interruption in hematopoiesis causes residual anemia, thrombocytopenia, and leukopenia. Production of leukocytes and platelets is inhibited to different degrees depending on the type of therapy administered. 6 The severity of neutropenia and thrombocytopenia is variable and often requires intervention.6 Patients who become anemic from chemotherapeutic erythroid marrow suppression have decreased oxygen transport related to an absolute deficiency in hemoglobin. 24 Myelosuppressive chemotherapy can have a profound effect on the perioperative treatment of the patient.6 Surgeon, anesthetist, and hematologist must remain in close communication to ensure safe, effective care.

Coagulation mechanisms may be dysfunctional because of impaired production or abnormal consumption of blood elements.6 Defects in coagulation often result from the use of anthracyclines, actinomycin, or plicamycin. Before surgery, the platelet count and coagulation profiles should be obtained so that appropriate blood products can be readily available. Platelets

in excess of 100,000/mm3 are considered adequate for essentially any surgical procedure.24 A window for performing surgery exists 2 weeks after therapy when marrow function has returned and new formed elements can be expected to be synthesized.24 Chemotherapeutic agents that produce myelosuppression-and destroy the cellular components of the inflammatory response-depress the immune system function, predisposing patients to infection.25 The duration of neutropenia is typically 8 to 10 days. Variations exist related to the nature and intensity of the chemotherapeutic treatment.26 Infection control practices require strict aseptic technique when anesthesia providers are asked to insert central lines, arterial lines, or peripheral intravenous lines. A septic patient may have hypovolemia, hypotension, increased metabolic rate, and fever.

Drug interactions

Cytochrome P-450 enzymes function in the biotransformation of cytotoxic and intravenous anesthetic agents, including opioids, benzodiazepines, and local anesthetics. A large number of P-450 enzymes are selectively induced by chemotherapeutic agents enhancing the rate of P-450 synthesis or reducing the rate of degradation.9 Therefore, enzyme induction may result in the acceleration of metabolism and may decrease the pharmacologic action. This induction of enzymes by cytotoxic agents is dose-dependent and reversible and leads to drug intolerance and clinically significant drug interactions.9 In the case of drugs metabolically transformed to reactive metabolites, enzyme induction may exacerbate metabolite-mediated tissue toxicity.

Thiotepa and cyclophosphamide produce a significant reduction in pseudocholinesterase activity, affecting the duration of action of drugs such as succinylcholine. Appropriate precautions such as avoidance of depolarizing relaxant agents should be taken with patients receiving cyclophosphamide and requiring general anesthesia. Plasma cholinesterase levels may take weeks to return to normal after being suppressed by drugs.27 Prolonged apnea after anesthesia in patients receiving cyclophosphamide may be treated with ventilatory support.28 Patients receiving chemotherapy, when exposed to anesthetic agents, are susceptible to a wide array of clinical drug interactions, necessitating vigilance by anesthesia providers.

Conclusion

In the role of anesthesia provider, distinguishing the anatomic and physiologic effects that occur with cancer chemotherapeutic treatment is paramount. Because of the high prevalence of cancer, anesthetists will frequently encounter patients receiving chemotherapy in their practice. It is crucial for anesthetists to understand how cytotoxic agents affect this population acutely and long-term. Understanding of the toxic effects of chemotherapy on different organ systems and their anesthetic drug interactions is vital for developing perioperative management strategies in anesthesia. Creating a tool, such as a preassessment form, focused on gathering cancer-specific treatment data would further refine patient-specific care. Accurate knowledge will assist in customizing provision of anesthesia to ensure a reduced risk of perioperative morbidity and mortality.

A COMPARISON OF PREOPERATIVE AIRWAY ASSESSMENT TECHNIQUES: THE MODIFIED MALLAMPATI AND THE UPPER LIP BITE TEST

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Discussion The purpose of this study was to compare the preoperative anesthetic airway evaluation methods of the modified Mallamapti test (MMT) and upper lip bite test (ULBT) with the direct laryngoscopic views obtained during tracheal intubation. Positive relationships were predicted for the MMT and ULBT with direct laryngoscopic view and between the MMT and ULBT. We assessed 50 patients' airways preoperatively by MMT and ULBT. Intraoperatively, laryngoscopic views were graded on the Cormack and Lehane scale. Descriptive statistics and correlations were computed.

There was no relationship between the MMT and the ULBT and the Cormack and Lehane scale. There was a significant relationship between the ULBT and the Cormack and Lehane scale ($r = 0.512$; $P < .001$). The ULBT was superior to the MMT in every measure in this study: sensitivity (55% vs 11%), specificity (97% vs 75%), positive predictive value (83%vs 9%), and accuracy (90%vs 64%).

The findings of this study support those of a previous study of the ULBT. Because of the ease of the ULBT and the promising results of this small study, we recommend further research with a larger, more diverse sample.

Key words: Airway assessment modified Mallampati test, upper lip bite test.

Of all anesthetic deaths, 30% to 40% are attributed to the inability to manage a difficult airway.1 Of the overall claims against anesthetists in the Closed Claims Project, 17% involved difficult or impossible intubation in which no preoperative airway assessment was

documented.2 In light of this, it is not surprising that the American Association of Nurse Anesthetists has established the preanesthetic assessment of the patient and the airway as the first standard of practice.3

Prediction of potentially difficult airway management during the preoperative period is determined by the anatomy of the oropharyngeal structures, architecture, and range of movement of the oropharnyx and neck. Clinical evaluation of these anatomical structures occurs by noting the atlanto-occipital joint extension, thyromental distance, and the modified Mallampati classification.4 The "sniffing" position or atlanto-occipital joint extension was first described in 1913 by Jackson and is believed to align the oral, pharyngeal, and laryngeal axes for a direct view of the glottic opening. Although the sniffing position is widely used, aligning the axes is based on observation alone and not on actual measurement of the angles of flexion and extension achieved. In fact, no scientific validation has been found demonstrating that this maneuver had any more significant effect on the laryngoscopy view over simple neck extension.5

The thyromental distance, or area between chin and thyroid cartilage, is defined as the distance from the thyroid cartilage to the tip of chin or mentum.4 The determination of the thyromental distance can be difficult in overweight patients, patients who are immobilized, and patients with goiters or other neck disease. Karkouti et al6 found the interobserver reliability was moderate relating to the thyromental distance assessment technique; moreover, thyromental distance was of little value in predicting a difficult intubation in adults.7

Another preoperative method to assess the presence of a difficult airway is the modified Mallampati test (MMT). This assessment determines the size of the tongue in relation to the oropharynx and the ability to open the mouth.8 Its classifications are based on observation of the pharyngeal structures with the mouth fully open and tongue maximally protruded. Mallampati et al8 found significant correlation between the ability to visualize pharyngeal structures and ease of laryngoscopy and intubation ($P < .001$). The literature indicates that the modified Mallampati classification has relatively high specificity but low sensitivity and a high number of false-positive results.9-11

The MMT has shown poor reliability in assessing oropharyngeal views.6 The lack of reliability could be due to discrepancies in administering, evaluating, and interpreting the test.

Because the assessment of the oropharyngeal anatomy requires an open mouth with tongue protrusion, patients with small mouth openings or altered levels of consciousness could be misclassified. The MMT, the sniffing position, and the thyromental distance do not consider the patient's dentition or variations in the degree of mandibular range of motion that may be present12; thus, the validity of each assessment is influenced by the experience and skill level of the anesthesia provider.6

Recently, a new technique to evaluate for difficult airway intubation was reported. The upper lip bite test (ULBT) was developed by Khan et al12 in an effort to produce a simple, single test that could be used preoperatively to evaluate for a difficult airway. The test is classified according to the ability to bite the upper lip with the lower teeth. The researchers state the anatomical distinction between the ULBT and the other preoperative airway evaluation methods lies in the range and freedom of movement of the mandible and the architecture of the teeth.12 In a sample of 300, the ULBT was found to have an accuracy of 88%, compared with 67.7% for the MMT, and the specificity of the ULBT for predicting easy intubation was 88.7% compared with 66.8% for the MMT.12

The ULBT takes into account some of the limitations associated with traditional airway evaluation methods. Interobserver reliability in distinguishing the oropharyngeal anatomy is negligible due to the simplicity in observation and performance of the test12; thus, its use is not dependent on skill or experience level. Although this technique shows much promise, limited data exist to support its widespread adoption as the method of choice for preoperative airway assessment.

Purpose

The purpose of this study was to compare the preoperative anesthetic airway evaluation methods of MMT and ULBT with the direct laryngoscopic views obtained during tracheal intubation.

* Hypotheses

1. There will be a significant direct relationship between the MMT and Cormack and Lehane scale.

2. There will be a significant direct relationship between the ULBT and Cormack and Lehane scale.

3. There will be a significant direct relationship between results of the ULBT and the MMT.

Methods

* Design. This was a prospective, comparative study evaluating the relationship between the 2 preoperative airway assessment techniques and glottic exposure obtained during orotracheal intubation. The interrater reliability was single blinded, that is, the anesthesiologist assessing glottic exposure was blinded to the preoperative airway, but the other investigators were not.

* Sample and setting. A power analysis was conducted assuming a moderate effect, a power of .80, and an α of .05. A sample size of 50 was determined to be appropriate for this study. A convenience sample of 50 participants scheduled for elective surgery under general anesthesia were selected from the surgical schedule of a large metropolitan level I trauma center located in the southeastern United States. Criteria for inclusion were: age 18 years or older and scheduled for an elective surgical procedure under general anesthesia requiring intubation.

To achieve more consistent physiological effects and scoring, we limited paralytic agents to one (vecuronium). Exclusion criteria included the following: (1) rapid-sequence induction of anesthesia (different muscle relaxants used); (2) inability to open the mouth due to existing trauma or medical condition, preexisting neck or facial disease causing distortion of the airway, edentulous, and/or a history of difficult intubation; (3) altered level of consciousness, confusion, or inability to follow commands; and/or (4) preexisting limitation or pain with cervical spine movement. Patients requiring rapid-sequence induction are already at high risk for aspiration; the airway should be rapidly secured with an endotracheal tube and not subjected to repeated or delayed assessment as might occur in the study.

* Protection of human rights. Permission to conduct the study was obtained from the university and the medical center. Written consent was obtained from participants in the preoperative holding area. Because all study procedures included usual and customary care, there were no additional risks to participants.

*** Operational definitions.**

MMT: A scale indicating the amount of posterior pharynx that can be visualized with the mouth open8: class I, visualization of soft palate, fauces, uvula, and pillars; class II, visualization of soft palate, fauces, and uvula; class III, visualization of soft palate and base of the uvula; and class IV, soft palate not visible. Classifications of III or IV were considered potentially difficult intubations. Assessments were conducted with the participant in sitting position at eye level to investigator with the mouth maximally open and tongue maximally protruded. The airway was examined twice with a flashlight and then graded.

ULBT: A scale indicating the range of motion and bite of the lower teeth onto the upper lip12: class I, lower incisors can bite the upper lip above the vermilion line, class II, lower incisors can bite the upper lip below the vermilion line, and class III, lower incisors cannot bite the upper lip. A classification of III was considered a potentially difficult intubation. This was assessed by having the participant in the sitting position at eye level to investigator. The ULBT was demonstrated by the investigator, performed by the participants twice, and graded.

Cormack and Lehane scale: A scale indicating the glottic view obtained with direct laryngoscopy13: grade I, full view of the glottis; grade II, glottis partially exposed, anterior commissure not seen; grade III, only epiglottis seen; and grade IV, epiglottis not seen. Grades III and IV were considered difficult intubations.

Outcome terms (Table 1): true-positive, a difficult intubation that was predicted to be difficult; false-positive, an easy intubation that was predicted to be difficult; true-negative, an easy intubation that was predicted to be easy; false-negative, a difficult intubation that was predicted to be easy; sensitivity, the percentage of correctly predicted difficult intubations as a proportion of all intubations that were truly difficult, ie, true-positives/(true-positives + false-negatives); specificity , the percentage of correctly predicted easy intubations as a proportion of all intubations that were truly easy, ie, true-negatives/(true-negatives + false-positives); positive predictive value, the percentage of correctly predicted difficult intubations as a proportion of all predicted difficult intubations, ie, true-positives/(true-positives + false-positives); negative predictive value, the percentage of correctly predicted easy intubations as a proportion of all predicted easy intubations, ie, true-negatives/(true-negatives + false-negatives); and accuracy,

the percentage of correctly predicted easy or difficult intubations as a proportion of all intubations, ie (true-positives + true-negatives)/ (true-positives + true-negatives + false-positives + false-negatives).

* Procedure. After written consent was obtained, participants were assessed in the preoperative holding area using the MMT and the ULBT. Two researchers collected all data (S.A.D. and S.W.W.). Participants received a standard induction sequence (vecuronium, 0.1 mg/kg; propofol, 1.5-2.5 mg/kg; fentanyl, 1-2 Âμg/kg; lidocaine, 1 mg/kg; isoflurane, 0.6% inspired concentration; and 100% oxygen). A laryngoscopy was then performed with a No. 3 or No. 4 MacIntosh blade after loss of train of four by using a nerve stimulator to stimulate the facial nerve. The laryngeal view was graded using the Cormack and Lehane scale. Interobserver reliability was assessed for the first 20 participants (10 subjects per investigator). An anesthesiologist with extensive experience in difficult airway classification and management was blinded to the 2 investigators' (senior nurse anesthesia student) classification of the airway. Strong reliability was established (K = 1.0).

Findings

The 50 participants included 19 men (38%) and 31 women (62%) with ages ranging from 18 to 85 years (mean, 44.3 years; SD, 13.149 years). African Americans represented 16% (n = 8), and 42% (n = 21)were white. Participant height ranged from 60 to 77 in (mean, 66.5 in; SD, 4.16 in), weight ranged from 54 to 139 kg (mean, 82.58 kg; SD, 18.41 kg), with body mass index (BMI) between 19.29 and 48.65 (mean, 29.1; SD, 6.8).

Table 2 shows the frequencies of classifications on the 3 airway assessments. There were 11 participants (22%) with an MMT grade of III and none with a grade of IV; 6 (12%) demonstrated a ULBT of III. A total of 17 participants were predicted to have a Cormack and Lehane graded scale of III and IV. A grade III or IV on the Cormack and Lehane scale was exhibited by 9 (18%); all were successfully intubated. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy are given in Table 3.

As participant height decreased, the MMT predicted intubation to be more difficult ($r = -0.377$; $P < .01$), but there was no relationship between the MMT and weight ($r = 0.191$; $P > .05$). There was a positive relationship between MMT and BMI ($r = 0.339$; $P < .05$). No

relationships were found between the ULBT and height (r = - 0.009; P > .05), weight (r = 0.046; P > .05), or BMI (r = 0.051; P > .05). There was a significant relationship between weight and the Cormack and Lehane scale (r = 0.283; P < .05) but not between the scale and height (r = 0.011; P > .05) or BMI (r = 0.26; P > .05).

The hypotheses were tested by using the Spearman rho (Table 4). No significant relationships were found between the MMT and Cormack and Lehane scale (r = 0.172; P > .05) or between the MMT and the ULBT (r = 0.223; P > .05). A significant direct relationship between the ULBT and Cormack and Lehane scale was demonstrated (r = 0.512; P < .001).

* Limitations. There were several limitations to the study. Data were collected from a single level I trauma center in the southeastern United States using a convenience sample. Thus, caution should be used when generalizing to other settings. Interrater reliability for the Cormack and Lehane scale was assessed only at the beginning of the study rather than episodically throughout. Nevertheless, the investigators were senior nurse anesthesia students who had been independently intubating for more than a year, and the Cormack and Lehane scale has limited subjectivity. Interobserver reliability was not assessed for the MMT. All participants were scheduled for elective surgery, and there were no participants with an ASA status of more than III. In additional, and importantly, the ULBT requires the patients' cooperation, ability to move the mouth, and the presence of teeth; only participants meeting those criteria participated.

* Findings. This study supported the findings of Khan et al,12 that the ULBT was superior to the MMT in specificity and accuracy of predicting difficult intubation. In addition, although Khan et al12 found no differences between the 2 assessments in sensitivity, positive predictive value, and negative predictive value, the present study found the ULBT to be superior to the MMT in all measures (see Table 3). Some of the differences between the 2 studies lie in the strength of the findings.

Proportionally, more patients in the present study (11 [22%]) demonstrated an MMT of III (predicted difficult intubation) compared with the previous study in which 4.6% were reported having classifications of III or IV. This may be because of the setting for this study-a level I trauma center that also provides most of the city's indigent care. A smaller difference in the percentage exhibiting a ULBT of III was found-12% (n = 6) for the present study vs 4.6% for the previous study. In the present study, 18% of the participants (9/50) had airways that were

difficult to intubate during laryngoscopy, as measured by the Cormack and Lehane scale. In contrast, Khan et al12 reported finding only 5.7% (17/300) of participants having a difficult intubation. In both studies, all intubation attempts were successful. This proportionally high level of difficult intubations may be accounted for by the nature of the agency in which the present study was conducted. The hospital is a tertiary center that serves a large region in the southeastern United States. Many of its patients are indigent and/or referred.

No relationship between MMT and the Cormack and Lehane scale was found. This was a surprising finding because the MMT has been recognized as the "gold standard"14 for many years and has been described as the primary airway assessment tool technique used in modern anesthesia practice.3 Mallampati et al8 reported using a convenient sample of 210 participants and 22 data collectors and finding a significant relationship between the ability to visualize pharyngeal structures and ease of laryngoscopy and intubation ($P < .001$). Interrater reliability was not reported; the large number of data collectors could have affected the reliability. In the present study, interobserver reliability was strong for the Cormack and Lehane assessments but was not conducted with the MMT.

The MMT requires anesthesia providers to recognize and identify the complex oropharyngeal anatomy to determine the appropriate level of classification. Discrepancies in administering, evaluating, and interpreting the MMT have been suggested by others when they found the MMT was not reliable in predicting a difficulty airway.6 Oates et al9 found the MMT to be a subjective instrument in predicting a difficult airway, with interobserver variations significantly altering the results. One factor cited as "critical" in achieving a reliable Mallampati score is the maximal extrusion of the tongue and opening of the mouth. The authors further state, "failure to apply this rigorously is a major pitfall when performing the assessment. They also concluded that the MMT score could be significantly altered with phonation and accessory muscle use, and the impact of the interobserver variation was significant in explaining the results. Other studies evaluating the Mallampati classification have shown this technique too insensitive when used alone. Savva11 found the MMT too insensitive and insufficiently specific for routine use (sensitivity, 64.7%; specificity, 66.1%; and positive predictive value, 8.9%). Savva11 found that other assessment tools, such as the sternomental distance, were more sensitive and specific than the Mallampati classification. Frerk10 concluded that the MMT used

as the sole preoperative assessment tool is sensitive but not very specific, finding that the high numbers of false-positive results prohibits it from being an accurate sole preoperative assessment tool. In the current study, 10 participants (20%) had false-positive findings for the MMT; Kahn et al12 found 33.2%.

In the present study, a strong correlation between the ULBT and Cormack and Lehane scale ($r = 0.512$; $P < .001$) was found; no significant relationship was found between the ULBT and the MMT. The ULBT showed a significantly higher specificity than theMMT (97% vs 75%, respectively) and accuracy (90% vs 64%, respectively), similar to results found by Khan et al.12 In comparing the positive predictive value, the ULBT predicted difficult intubations correctly 83% of the time, whereas theMMT predicted a difficult intubation only 9% of the time. In contrast, Khan et al12 reported positive predictive values for the ULBT and MMT as 28.9% and 13%, respectively. Demographic variables of the participants were not reported in the original study, and significant differences in weight and/or height between participants in the 2 studies may have existed.

USE OF HELIOX FOR INTRAOPERATIVE BRONCHOSPASM: A CASE REPORT

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Bronchospasm is an anesthetic emergency that can lead to disastrous outcomes if treatment is irresolvable. An anesthesia provider must immediately initiate treatment if bronchospasm is suspected in order to avoid negative sequelae. The following is a case report of a 32-year-old man who experienced refractory bronchospasm upon emergence from general anesthesia.

This article discusses the initial treatment attempted at resolving the bronchospasm, as well as the use of heliox in the ultimate resolution of the bronchospasm. Although heliox has been used for years to treat patients with various respiratory complications, it is not currently a common treatment instituted by anesthesia practitioners for the treatment of bronchospasm. Consideration of the use of heliox may provide another option for the treatment of a patient suffering from refractory bronchospasm.

Key words: bronchospasm, density, emergence, heliox, turbulence.

Bronchospasm can be a serious event that can lead to critical hypoxemia with ultimate brain damage or death.1-3 Although there is an increased incidence of bronchospasm in patients with preexisting respiratory conditions, such as asthma or chronic obstructive pulmonary disease, it is essential to remember that severe bronchospasm can occur in any patient regardless of medical history.1-2 It is imperative that the anesthesia provider recognize the signs and symptoms of bronchospasm. The clinical features of bronchospasm may resemble endobronchial intubation, obstruction of the endotracheal tube secondary to increased secretions or blood, pulmonary aspiration, pneumothorax, a kinked endotracheal tube, or pulmonary edema.2

Once bronchospasm has been identified, it is essential for the anesthesia provider to initiate treatment to prevent any adverse complications related to hypoxemia. Current therapies

for the management of bronchospasm include, but are not limited to, increasing inspired oxygen concentrations (FiO 2), alterations of ventilatory settings, eliminating suspected causative antigens, deepening the general anesthetic, bronchodilator therapy or other pharmacological therapy to decrease parasympathetic reflexes, or deep extubation. 2 An anesthesia provider must quickly consider alternatives to refractory bronchospasm. This case report presents the use of heliox as another alternative for the management of refractory bronchospasm.

Case summary

A 32-year-old man presented for an emergency appendectomy. A preoperative anesthesia evaluation was completed in the emergency department revealing a 1-pack-per-month smoking history with no other significant medical history. The patient denied any regular medications, allergies, or history of any previous surgery. He was unaware of any familial history of anesthetic complications. Assessment of the airway revealed a class I Mallampati score, with greater than 3 fingerbreadths thyromental distance and adequate mouth opening. Native dentition was intact and he demonstrated full cervical range of motion. Laboratory studies were within normal limits. The patient's height was 61 inches (155 cm), and he weighed 187 pounds (84 kg). Preoperative vital signs were as follows: blood pressure, 140/65 mm Hg; heart rate, 65 beats per minute; tympanic membrane temperature, 37Â°C; and room air oxygen saturation (SpO 2), 100%. Upon auscultation, breath sounds were clear bilaterally. A physical status II was assigned, and the patient was given midazolam intravenously for preoperative sedation and sodium citrate/citric acid by mouth as he was wheeled to the operating room. Preoperative antibiotics started in the emergency department included ceftriaxone and metronidazole.

Upon arrival in the operating room, standard monitors were applied. The patient was preoxygenated for 5 minutes with 100% FiO 2 per breathing circuit face mask. A rapid sequence induction with cricoid pressure was performed using fentanyl, lidocaine, sodium thiopental, and succinylcholine. An atraumatic laryngoscopy was performed revealing grade I visualization of the vocal cords. A 7.5-mm cuffed endotracheal tube was inserted in the trachea on the first attempt, and the tube was secured at 21 cm at the lip after confirmation of tube

placement via detection of end-tidal carbon dioxide and auscultation of clear bilateral breath sounds.

Respirations were controlled with mechanical ventilation, and general anesthesia was maintained with 100% FiO 2 and isoflurane 1% to 1.5% end-tidal concentration. Vecuronium, 4 mg, was given during the procedure for muscle relaxation with an uneventful anesthetic. Approximately 30 minutes before the end of surgery, nitrous oxide was initiated at a 50% inspired concentration. Upon closure of the skin, neuromuscular blockade was antagonized with neostigmine, 3 mg, and glycopyrolate, 0.5 mg, and the response to double-burst stimulation exhibited 2 strong contractions without fade. Nitrous oxide and isoflurane were terminated and 100% FiO 2 was reinitiated. As end-tidal isoflurane concentrations decreased to approximately 0.24%, the patient began to cough. Oxygen saturation quickly dropped to 60%, and circumoral cyanosis was present. Tube placement was confirmed with auscultation of the lungs revealing severely diminished bilateral breath sounds. Positive pressure manual ventilation delivered tidal volumes of 200 mL with peak airway pressures greater than 50 cm H2 O pressure. Severe bronchospasm was suspected. Twelve puffs of albuterol (90 Âµg/puff) were given via the endotracheal tube. Isoflurane was reinstituted, lidocaine, 50 mg, was given intravenously, and subcutaneous epinephrine, 100 Âµg, was administered. Hemoglobin saturation with oxygen increased to 94% within approximately 1 minute after deepening of the volatile agent and peak airway pressures decreased to 39 cm H2 O pressure. A second emergence was attempted, and once again bronchospasm ensued after the patient coughed. Saturation decreased briefly to 60%. Bronchospasm resolved with the deepening of the volatile anesthetic and administration of albuterol per endotracheal tube and subcutaneous epinephrine. Saturation improved to 94% as isoflurane end-tidal concentration increased to 0.48%. The third emergence was unsuccessful, resulting in a saturation of 70% accompanying bronchospasm. Again, isoflurane concentration was increased, 12 puffs of albuterol were administered via the endotracheal tube, and 100 Âµg subcutaneous epinephrine was given, with saturation improving to 95%.

A request was made to the Respiratory Therapy Department to obtain a heliox tank. Isoflurane was discontinued, and a 70%/30% helium-oxygen mixture was administered via a Jackson-Reese circuit with assisted ventilation. Tidal volumes rapidly increased from 200 mL to 400 mL. The patient initiated a regular respiratory pattern with a rate of 24 breaths per minute.

Saturation was maintained between 94% and 97%. The patient opened his eyes and began to cough, and the trachea was extubated after endotracheal cuff deflation. The patient maintained his airway and 100% FiO 2 was delivered via simple face mask. Auscultated breath sounds revealed mild expiratory wheezes. Saturation remained at 98%. The patient was taken to the recovery room where an albuterol nebulizer was immediately instituted. The patient experienced no further respiratory complications and was discharged home on postoperative day 2 with no respiratory sequelae.

Discussion

Bronchospasm is a relatively infrequent occurrence during anesthesia. According to Olsson,3 who in 1986 completed a restrospective study of 136,929 surgical patients, the incidence of bronchospasm during anesthesia is 1.6 per 1,000 anesthetics. Bronchospasm is a result of extreme contraction of the bronchial smooth muscle that leads to narrowing and increased resistance of the airways. The autonomic nervous system is responsible for controlling the muscle tone by balancing the levels of 3'5'-cyclic adenosine monophospate (cAMP) and 3'5'-cyclic guanine monophosphate (cGMP). The sympathetic nervous system is responsible for increasing cAMP levels through epinephrine-induced β^sub 2^ adrenergic receptor stimulation resulting in bronchodilation.2 The parasympathetic nervous system, through stimulation of muscarinic receptors or vagus nerve activity, is responsible for bronchoconstriction. Some biochemical mediators (prosta-glandins, leukotrienes), pharmacological therapies (cholinergic agonists, histaminics), and other noxious stimuli (mechanical stimulation, secretions) also are probable antagonists of bronchial lumen patency. Bronchospasm can be difficult to detect under general anesthesia,2 and it may manifest in several ways. Coughing, increased peak airway pressures without change in plateau pressures, or a decreased phase II slope on the capnogram are all possible signs. Wheezing is a common sign; however, airway resistance may be so great that wheezing may not occur indicating extremely low gas exchange.2

Airway resistance increases dramatically as the bronchial lumen narrows, as derived from Poiseuille's law: R= $8\eta l/\pi r$^sup 4^ (R indicates resistance, . indicates viscosity, l indicates length of tube, and r indicates radius of the tube).4 Therefore, bronchoconstriction that reduces the airway diameter by half is capable of producing a 16-fold increase in resistance. Turbulent

flow in the airways also contributes to the increased airway resistance subsequent to bronchospasm. Turbulent flow is indicated by a Reynold's number (Re) greater than 2000.4 Reynold's number is defined as: Re=2rvd/ή (d indicates density, v indicates average velocity, r indicates radius, and . indicates viscosity).4 Thus, decreasing the density of a gas lowers Reynold's number achieving a more laminar flow in the airway.

Helium, a biologically inert gas, has a density of one eighth that of nitrogen and oxygen.5 The density of air is approximately 1.20 kg/m^sup 3^. The density of 100% oxygen is approximately 1.33 kg/m^sup 3^. The density of a nitrous/oxygen mixture is approximately 1.41 kg/m^sup 3^. The density of a 70%/30% heliox mixture is approximately 0.52 kg/m^sup 3^. Heliox, the combination of helium and oxygen, therefore has a reduced density compared to air.6 An 80%/20% helium-oxygen mixture has a density one third that of air-oxygen mixture. 7 This significantly reduced density is capable of decreasing airway resistance by promoting laminar flow. The use of helium-oxygen mixtures for various respiratory complications began in 1934.5 To date, heliox is not routinely used as primary treatment for any respiratory ailment perhaps because of the lack of research studies confirming its effectiveness. Throughout the years since its discovery, it has been used to aid in treating conditions such as asthma, chronic obstructive pulmonary disease, and upper airway obstruction.5 Studies are lacking for the use of heliox in bronchospasm experienced during anesthesia.

Heliox has been shown to be beneficial in the treatment of upper airway obstruction by reducing airway resistance.8-9 In a study by Kemper et al,8 postextubation stridor scores were significantly lowered with the use of heliox therapy compared to the use of standard oxygen-enriched air. In this double-blind, randomized, controlled crossover trial, helium was found be safe and effective for the treatment of postextubation respiratory distress.8 From this study it appears that heliox could be considered before reintubation or other airway manipulation to improve ventilation in certain situations of unresolved partial upper airway obstruction. Another study by Lu et al9 also demonstrated the successful use of heliox in treating upper airway obstruction. Simulating a case study of a right pneumonectomy, they occluded the right mainstem bronchi of 6 dogs. After the right mainstem bronchus was occluded, they proceeded to partially occlude the left mainstem and initiate heliox therapy in incremental doses. The peak airway pressure and PaCO 2 were both reduced with the addition

of heliox therapy thus improving ventilation. Heliox may be beneficial for preventing prolonged mechanical ventilation or respiratory failure associated with negative outcomes.

Asthma, a condition marked by recurrent spasmodic constriction of the bronchi, is a disease that can pose significant challenge to the anesthesia provider. The incidence of bronchospasm and other perioperative respiratory events is increased in patients with this condition.10 A serious bronchospasm can present in a patient with a history of asthma at any time. If severe, sometimes routine pharmacological therapy is insufficient and other treatment is crucial to avoid a negative outcome.10 Heliox has been shown to be therapeutically effective and beneficial in treating asthmatics in several anecdotal case studies.5,10-13 In a restrospective case-match control design, Schaeffer et all1 compared oxygenation in 22 mechanically ventilated patients suffering from status asthmaticus. Eleven patients who received heliox therapy after intitation of mechanical ventilation were compared with 11 patients in a control group that did not receive heliox. They found that a brief period of heliox administration during mechanical ventilation in status asthmaticus significantly improved oxygenation and decreased the alveolar-arterial gradient. Current literature clearly indicates the need for prospective, reliable clinical studies regarding the use of heliox with asthmatics.5,12-13 Review of the literature demonstrates that heliox can be beneficial in reducing peak inspiratory pressures and decreasing pulsus paradoxus (which is suggested to indicate decreased work of breathing). Heliox also may be capable of promoting the delivery of an inhaled β-agonist to the distal airways thus facilitating the desired action.5 Controversy exists in the interpretation of these studies, and further research is needed to confirm the efficacy of heliox therapy in asthma.

There is no documented literature about the use of heliox for the treatment of bronchospasm under general anesthesia. In a case report by Polaner,14 heliox was used in conjunction with a laryngeal mask airway for a child with compression of his carina and left mainstem bronchus due to an anterior mediastinal mass. In this specific case, heliox administration preoperatively increased the patient's SaO 2 from 76% to 96%.14 Heliox was continued intraoperatively and contributed to the successful outcome of the patient.14 In the current literature, heliox appears to be safe and effective in appropriately selected patients. Research may be indicated for the use of heliox therapy in general anesthesia.

In the present case study, the use of heliox allowed emergence from general anesthesia with tidal volumes adequate for extubation. The bronchospasm may have been caused by the reversal agent, by the mechanical stimulus of the endotracheal tube, or by a number of other biochemical mediators or triggers. Clinically, bronchospasm resolved following removal of the endotracheal tube. Theoretically, the heliox promoted laminar flow in the airway, reducing the effect of the bronchospasm. Successful extubation may have removed a potent stimulus allowing resolution of the event. Additional studies are needed to address the possible benefit of heliox administration in management of bronchospasm under general anesthesia.

It is prudent for the anesthesia provider to integrate knowledge of pharmacology and physiology of heliox into current practice. Heliox is relatively inexpensive when used in short increments of time. Heliox is not readily available in all institutions, however.When faced with a severe bronchospasm, detection and treatment must be instituted rapidly. If a bronchospasm is resistant to standard therapy, other alternatives must be initiated to prevent life-threatening sequelae. Heliox therapy may contribute to effective management of brochospasm under general anesthesia in the appropriate patient.

A COMPARATIVE ANALYSIS OF ISOPROPYL ALCOHOL AND ONDANSETRON IN THE TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING FROM THE HOSPITAL SETTING TO THE HOME

From:

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Postoperative nausea and vomiting (PONV) are among the most common and distressing symptoms that occur following surgery. Often, a patient will report that the psychological and physical distress experienced secondary to PONV were the worst part of the entire surgical experience.1,2 Several individual patient and surgical factors have been identified that predispose a patient to PONV. The individual patient factors include age, gender, weight, amount of stomach contents, motion sickness, a history of nonsmoking, prior PONV, and presence of inner ear pathology.1,2 Surgical factors include the length of surgery (>60 minutes), type of surgery performed (gynecologic and laparoscopic), type of anesthesia administered (general vs regional), degree of hypotension experienced, opioid requirements during and following the procedure, and the amount of postoperative pain.1,2 Based on these findings, anesthesia practitioners have customized anesthetic management plans that include controlling for some of the factors and administering prophylactic antiemetic agents to patients who are at high risk for PONV. Despite these anesthetic treatment plans, the overall incidence can remain as high as 50% in certain patient populations.1,2

In addition to the problem of the patient's psychological and physical discomfort that can result from PONV, other complications may occur secondary to PONV. These include aspiration of stomach contents, dehydration, electrolyte disturbances, and interruption of the surgical incision. In addition, PONV can have a major impact on healthcare delivery-it has been noted that patients who experience PONV tend to require longer hospitalization and have a

delayed return to the workforce, so PONV acts as a conduit for driving up the cost of healthcare.2,3

The exact mechanism of PONV is poorly understood. It is hypothesized that the nausea response is coordinated via a central vomiting center (VC) in the medulla called the chemoreceptor trigger zone (CTZ). When stimulated by noxious substances, receptors relay the information to the vomiting center, which then acts on the efferent pathways, initiating vomiting. The CTZ is located in the highly vascularized area on the brain surface that is lacking a real blood-brain barrier; therefore, it can react to neurotransmitters involved in eliciting an emetic response. These neurotransmitters include serotonin (5-HT^sub 3^), dopamine, histamine (H^sub 1^), and acetylcholine. It has been shown that blockade of one or more of these neurotransmitters at the level of CTZ decrease the incidence of PONV. Specific pharmacological agents have been developed that successfully block the transmission of these neurotransmitters at the level of the CTZ; however, there is no single agent identified that will block all pathways.4 To offset this, many practitioners use a combination of neurotransmitter antagonists to block more than one pathway, an approach shown to be more successful than use of separate agents. However, using a monomodal or multimodal pharmacological approach to treat PONV can result in profound sedation and hypotension, resulting in increased morbidity. Therefore, alternative methods to treat PONV that have little to no impact on patient sensorium or vital signs need to be found.

Most health professionals would agree that the best PONV treatment should be cost-effective, self-administered, and cause few to no side effects. One such treatment modality that seems to have all of these characteristics is inhaled isopropyl alcohol (IPA). Several studies have reported the clinical efficacy of inhaled IPA in the treatment of PONV. Most notable are the studies by Wang et al,5 who found that the inhalation of IPA in children was effective in achieving transient relief of motion related nausea, and Winston et al,6 who found that inhaled IPA was as effective in the treatment of PONV as ondansetron but also worked considerably faster in alleviating PONV symptoms. However, limitations noted in both studies were that IPA was only clinically effective for a short time and that subsequent treatments were often required to adequately treat PONV. In addition, these studies were designed to analyze IPA efficacy in a very limited setting (during transport and in the postanesthesia care unit [PACU]), and it was

unclear whether IPA would be effective beyond these limited uses. Therefore, the purposes of this study were to validate the results reported by Winston et al6 and to determine whether IPA was just as effective through a patient's entire hospitalization and in the home setting.

Methods

Once institutional review board approval was obtained, a prospective, randomized study was conducted with 100 women, ASA physical status I, II, or III, ages 18 to 65 years who were scheduled for laparoscopic same-day surgery. Patients were excluded from the study if they had recent upper respiratory tract infections, inability or impaired ability to breathe through the nose, or history of hypersensitivity to IPA, 5-HT^sub 3^ antagonists, promethazine, or any other anesthesia protocol medication. Patients also were excluded if they reported using an antiemetic within 24 hours of surgery; were pregnant or currently breast-feeding; had a history of inner ear pathology, motion sickness, or migraine headaches; or were taking disulfiram, cefoperazone, or metronidazole. Once it was determined that a patient was eligible for inclusion and agreed to participate in the study, the patient was randomly assigned to the control group or the experimental group by using a computer-generated random numbers program.

Following informed written consent, a baseline 0 to 10 verbal numeric rating scale (VNRS) score, in which "0" indicated "no nausea" and "10" indicated the "worst imaginable nausea," was obtained and recorded. Demographic information also was obtained, including age, height, weight, race, and type of surgery. All subjects were prepared for surgery using standard operating procedures that included intravenous (IV) cannulation, prehydration with crystalloid solution, and anxiolysis with midazolam up to 5 mg IV at the discretion of the provider.

Subjects were then transported to the operative suite where standard monitors were placed, including a noninvasive blood pressure device, an electrocardiogram monitor, and pulse-oximetry and capnography devices. All subjects were then administered 100% oxygen via face mask for 5 minutes before induction of anesthesia. Administration of IV lidocaine up to 1 mg/kg; propofol, 1.5 to 2.0 mg/kg; fentanyl up to 5 Âµg/kg; and a nondepolarizing or depolarizing muscle relaxant of choice were used to induce anesthesia. Following induction, the

trachea was intubated and an orogastric tube placed to decompress the stomach. The orogastric tube was removed immediately before extubation of the trachea.

Maintenance of anesthesia was accomplished using desflurane, isoflurane, or sevoflurane in combination with a 50% nitrous oxide-oxygen mixture or a 50% oxygen-air mixture. In addition, all subjects were given up to 5 Âµg/kg of fentanyl IV to maintain analgesia. Approximately 15 to 30 minutes before the end of the surgical procedure, all subjects were given 30 mg of IV ketorolac. If required, neuromuscular blockade was reversed using neostigmine, 0.05 mg/kg IV, and glycopyrrolate, 0.01 mg/kg IV. All subjects were transferred to the PACU after extubation. All preoperative and intraoperative medications that were administered were noted and recorded on a data collection sheet.

While in the PACU, the nursing staff was instructed to treat any incidence of shivering with 12.5 mg of meperidine and complaints of pain with 1 to 3 mg of IV morphine sulfate (up to a maximum of 0.15 mg/kg). The PACU personnel were instructed to note time, dose, and effectiveness of all analgesics on the data collection sheet.

In addition to the baseline measurement of the VNRS score for nausea, an additional VNRS score was obtained for all subjects on emergence from anesthesia and at any time they complained of nausea. If a subject complained of nausea, VNRS scores were obtained on initial complaint, every 5 minutes following treatment for 30 minutes, and every 15 minutes thereafter until discharge from

For subjects assigned to the ondansetron (control) group, nausea was treated with ondansetron, 4 mg IV, every 15 minutes, up to an 8-mg maximum total dose. The PACU personnel were instructed to record the time, dose, and the VNRS scores on the data collection sheet. For subjects assigned to the IPA (experimental) group, nausea was treated by having the PACU nursing personnel hold a folded alcohol pad approximately Â½ inch from the opening of the patients' nares and instructing the patient to take 3 deep breaths of the vapors in and out through the nose. The IPA treatments were ordered to be administered on an as needed basis, every 5 minutes, up to a total of 3 administrations. All PACU personnel and subjects were instructed as to the specific use of the IPA and the parameters of the study before the initiation of the study.

Following discharge from the PACU, all subjects were transported to the same-day surgery unit (SDSU). The SDSU nursing personnel were instructed about the specific parameters of the study and protocols before initiation of the study. For complaints of nausea, SDSU personnel were instructed to use the same treatment regimen as that used in the PACU, including the administration of ondansetron, IPA, and recording of VNRS scores for nausea. In case nausea persisted in the ondansetron group following a total IV dose of 8 mg of ondansetron (cumulative amount between PACU and SDSU), nursing personnel were instructed to administer a 25-mg promethazine suppository. If nausea was refractory to treatment in the IPA group, all nursing personnel were instructed to treat nausea with ondansetron, 4 mg IV, every 15 minutes, up to a total dose of 8 mg. All complaints of nausea and treatment regimens used were recorded on a data collection sheet.

Following discharge from the SDSU, all subjects were discharged to home with a data collection tool on which they were asked to record nausea and vomiting events, what treatment was used, and clinical effectiveness of the treatment. Subjects were asked to record this data for a period of 24 hours.

Before discharge from the hospital, all subjects were given two 25-mg promethazine suppositories and instructed on self-administration. All subjects were given written and verbal instructions concerning treatment of PONV at home. Subjects randomized to the ondansetron group were asked to treat episodes of nausea and/or vomiting at home by self-administration of one 25-mg promethazine suppository every 6 hours as needed. Subjects randomized to the IPA group were asked to take 3 deep inhalations from an IPA pad every 15 minutes as needed to a maximum of 3 inhalational treatments. If the IPA was not working to the subject's satisfaction, or if 3 treatment regimens had been performed, IPA subjects were asked to self-administer a 25-mg promethazine suppository every 6 hours as needed, not to exceed 2 administrations. In addition, all subjects were asked to note the time of administration and the time they "felt relief" following administration. Before discharge from the hospital, all subjects in both groups were given instruction concerning the use and administration of promethazine suppositories.

All home data collection information was obtained and recorded by 2 investigators (J.W.C and L.R.R.) approximately 24 hours following discharge via a postoperative telephone interview. In addition, all subjects were asked to rate their anesthesia experience using a 4-point

ordinal scale in which a score of 1 indicated a "poor" experience, 2 indicated a "fair" experience, 3 indicated a "good" experience, and 4 indicated an "excellent" experience.

Before initiation of the study, a power analysis was performed based on previous studies that indicated that at 5 minutes following treatment, VNRS scores would decrease from a mean of 5.0 at baseline to a mean Â± SD of 4.5 Â± 2.7 in the ondansetron group and 2.1 Â± 2.5 in the IPA group. This indicated a sample size of only 15 subjects per group would be required to show significance when an a of .05 and a ÃŸ of .20 were used. However, it was assumed that only approximately 30% of the population as a whole would have complaints of PONV; therefore, the sample size was adjusted; 50 subjects per group would be required to show significance. All data were analyzed for entry errors, missing data, and consistency before statistical analysis. Statistical analysis was performed using SPSS statistical software (version 11.0, SPSS, Chicago, Ill). The VNRS scores were analyzed with the Student t test; demographic data and frequency data were analyzed using a χ^sup 2^ test. Satisfaction scores were analyzed using a Mann-Whitney U test. A P value of less than .05 was considered significant.

Results

Of the 100 subjects enrolled, 28 were disenrolled due to failure to adhere to protocol. Protocol violations included 12 subjects in the ondansetron group who were given IPA treatments in SDSU, 6 subjects given other antiemetic agents in the PACU before IPA treatments, and the remaining subjects losing their IPA or promethazine following discharge to home. This left a total of 72 subjects for study (34 control and 38 experimental). Of the 72 subjects, 68 underwent laparoscopic gynecologic procedures, and 4 had other general surgery laparoscopic procedures. Demographic characteristics with regard to age, weight, height, anesthesia times, and PACU and SDSU times were similar between groups (Table). When the intraoperative and postoperative analgesics given, the concentrations of volatile agents administered, and IV medications used were analyzed separately, no significant differences were noted between groups. ($P > .05$).

Nausea events reported in the PACU included 5 subjects (15%) in the control group and 8 subjects (21%) in the experimental group who required treatment. No subject in either group had an emetic event in the PACU or SDSU. Nausea events reported in the SDSU

included 15 subjects (44%) in the control group and 21 subjects (55%) in the experimental group who required treatment. We noted significant differences between groups when times to a 50% reduction in VNRS scores were analyzed for the first and second treatments. For the first treatment of PONV symptoms, subjects in the control group required a mean Â± SD of 33.88 Â± 23.2 minutes to achieve a 50% VNRS score reduction compared with 15.00 Â± 10.6 minutes for the experimental group (P = .011). Similar results also were noted for second treatments: the control group required a mean Â± SD of 26.25 Â± 7.5 minutes to achieve relief as opposed to 15.00 Â± 5.25 minutes for the experimental group (P = .013) (Figure 1). Only 1 subject (IPA group) reported 3 separate PONV events; therefore, no analysis was performed on time to alleviation for the third nausea event.

When the incidence of subjects requiring rescue treatment in the SDSU was analyzed, it was noted that 13 (38%) of the control group required rescue treatment, whereas only 10 (26%) of the experimental group required rescue treatment (P = .319). A total of 21 subjects reported nausea events at home (10 control; 11 experimental); however, 5 subjects in the control group reported using promethazine for rescue treatment compared with only 1 subject in the experimental group (P = .064) (Figure 2). All remaining subjects in the IPA group reported that their PONV at home was adequately treated by self-administration of IPA. No significant difference was noted when satisfaction scores for anesthesia experience were analyzed: both groups reported scores of 3 (good) or 4 (excellent) when quantifying their overall anesthesia experience (P > .05).

THE ICARUS EFFECT: THE INFLUENCE OF DILUENT WARMING ON DANTROLENE SODIUM MIXING TIME

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Prompt administration of intravenous (IV) dantrolene sodium (DS) is the primary determinant of successful treatment of malignant hyperthermia (MH) syndrome. Because DS has a long reconstitution time for use in treating an MH crisis, we evaluated an alternative technique for hastening the reconstitution.

Simulating real-world conditions, with equipment common to the operating room environment, We conducted a randomized, controlled, single-blind study dividing 16 DS vials into 2 equal groups: warm (41°C) and ambient temperature (22°C). With an IV fluid warmer at 41°C, primed with a 1-L bag of preservative-free sterile water, attached to a 60-mL syringe via a 3-way stopcock, we aspirated and injected the diluent directly into each DS vial.

The Icarus effect was clearly demonstrated: warmed diluent vs ambient temperature hastened the reconstitution time for DS. The mean time to particulate-free DS solution suitable for IV injection with the warm diluent was 58.88 seconds compared with 93.87 seconds for the ambient temperature group (P<.001). A practical method using a reliable and safe warming device readily available to anesthetists and ubiquitous to the operating room environment speeds the time to administration of DS ultimately reducing morbidity and mortality associated with MH.

Key words: Dantorlene sodium, diluent temperature, Icarus effect, particulate-free, malignant hyperthermia.

The diagnosis of malignant hyperthermia (MH) necessitates keen observation followed by swift intervention to reduce associated morbidity and mortality. Succinylcholine

and poten inhalational anesthetics can precipitate this devastating pharmacogenetic abnormality. The onset of MH signals the creation of a hypermetabolic state characterized by the disruption of calcium homeostasis in skeletal muscle, which, if not promptly corrected, culminates in death of the patient. Proper identification of MH-susceptible patients and avoidance of triggering agents are fundamental to a safe perianesthetic course. The key to effectively managing an MH crisis includes the rapid administration of dantrolene sodium (DS).

Since its introduction into clinical practice in 1979, the hydentoin derivative, DS, continues to function as first-line therapy against MH.[1] Its widespread use has drastically reduced mortality from nearly 80% in the 1970s to less than 10% today.[2] By inhibiting calcium release from the defective ryanodine type 1 receptor, DS effectively impairs excitation-coupling, leading to resolution of MH by restoring intracellular calcium balance.[3-5] Additional uses of DS include treatment for neuroleptic malignant syndrome, muscle spasticity, and, possibly, Ecstasy intoxication.[1]

The DS molecule is highly lipophilic, which prohibits expedient reconstitution with aqueous diluent. The intravenous (IV) DS formulation is supplied in 70-mL glass vials that contain the following mixture: 20 mg of lyophilized DS, 3 g of mannitol, and sodium hydroxide. The basic additive yields a final pH 9.5 after reconstitution with 60 mL of preservative-free sterile water.[6] Only preservative-free sterile water should be used to reconstitute DS. The addition of 3 g of mannitol offers renal protection against myoglobinemia and increases the solubility of DS in the aqueousdiluent.[1] Despite this advantage, DS remains a challenging drug to reconstitute and a direct consequence, this labor-intensive process comprises the rate-limiting step in DS administration.

The idea of adjusting temperature to impact the solubility of a substance is hardly revolutionary, and so we cite the tragic tale of Icarus. This mythical story serves as a testament to the ancient Greeks' understaning of the sophisticated nature of physics by illustrating the important relationship between the effect of temperature and the corresponding state of matter. As the story goes, Daedalus and his son Icarus were determined to escape their imprisonment within the Labyrinth of King Minos. Daedalus plotted a clever escape by fashioning 2 pairs of wings to allow them to fly free from their site of captivity on the Isle of Crete to mainland Greece. Icarus father cautioned his son not to journey too closely to the sun above or the ocean

below. Soon after taking flight, Icarus found himself elated by newly acquired ability. He failed to heed his father's advice as he unwarily ascended toward the heavens. The sun's radiating heat melted the wax which Icarus' wings were bound, leaving the child to unexpectedly plummet to his death in the raging sea beneath him.

By appreciating the legend of Iacarus, which clearly exemplifies the Newton Second Law of Thermodynamics, we postulated that warming the aqueous diluent would hasten the development of a clear and particulate-free DS mixture suitable for IV injection. In their elegantly designed study, Mitchell and Leighton[7] examined this concept despite the shortcoming that their study included only 1 data point at 5 temperatures between 20°C. Although they determined the presence of a linear relationship between diluent temperature and solubility, their study lacked the power to adequately support the significance of their findings. After we collected the datafor the present study in May 2006, Quraishi et al[8] reported similar findings in August 2006.

This randomized, controlled study aimed to identify whether sterile water warmed to 41°C hastens DS solubility compared with sterile water at the ambient operating room temperature of 22°C We devised a study with a sufficiently powered sample size, as revealed by the Cohen d calculation and based on previously published research, and a method for warming the diluent using materials common to the operating suite and readily available to anesthetists.

Materials and methods

We conducted a randomized, controlled, single-blind study in a closed operating room suite at Virginia Commonwealth University Health Sciences Campus, Richmond, Va. Because we had a finite quantity of DS vials, we conducted a pilot study before our formal study to test and refine our methodology.

We used equipment common to the operating room to best replicate the clinical environment. We prepared 2 Smith Industries Medical System (Rockland, Mass) Hotline fluid warmers (reference HL-90, 115V) with the following: a 1-L bag of preservative-free sterile water, 10 gtt/mL IV tubing, an 8-ft Hotline tubing (reference L-70, 0403), a 3-way stopcock, and a 60-mL syringe (Figure 1). One fluid warmer was designated for the warm group (41°C)

and the other for the ambient temperature group (22°C), which remained unplugged from the electrical wall outlet. We primed each circuit with preservative-free sterile water and used a 60-mL syringe connected to a 3-way stopcock at the distal end of the circuit to aspirate the diluent. We recorded all temperature measurements with a thermo resistor (reference 81-010400) Skin Temperature Sensor 400 Series (Smiths Medical, Rockland, Mass) connected to a Drager Infinity Delta Monitor (Delford, Pa). Room temperature was determined by exposing the thermo resistor skin temperature sensor to air for 1 minute. Baseline Hotline tubing measurements were obtained by purging eachciruit of its 20-mL priming volume, waiting 2 minutes, and inserting the temperature probe into the distal end of the circuit and allowing 1 minute to record the temperature. Before our study, we found that the temperature probe would elicit a stable reading in less than 1 minute; thus, we chose 1 minute to standardize our process. The mean temperatures for the warm and ambient temperatures for the warm and ambient temperature groups were 41.0°C and 22.3°C, respectively. We used a digital stopwatch to record all time-sensitive events.

We randomly divided 16 DS vials into 2 equal groups, a warm group (41°C) and an ambient temperature group (22°C). We constructed 16 slips of paper, H for "warm" and C for "ambient temperature," placed them in a bag, manually shuffled them within the bag, and withdrew 1 slip of paper at a time with the individual's head turned away from the bag at the time of drawing. The drawn slip of paper was discarded after its first and only use. We blindly withdrew the group assignment marker, purged the circuit of its 20-mL priming volume, waited 2 minutes, and then measured the diluent temperature via the distal end of the circuit for 1 minute. We connected a 60-mL syringe to the 3-way stopcock at the distal end of the fluid warmer, aspirated 60 mL of sterile water, and forcefully injected a full 60 mL into the DS vial.

One member of our research team was designated as the observer. During the pilot study, we incorporated a test trial of several randomly selected DS vials to train the observer to identify particulate vs particulate-free solutions suitable for IV injection (Figure 2). The observer was blinded to the aspiration of fluid and temperature measurement technique, and then was permitted to view the DS vial after it was injected with sterile water (time = 0). At no time was the observer allowed to touch the bottle to determine its temperature. A designated manual agitator performed a continuous series of mixing the vial by hand. This person

vigorously agitated the vial in an up-and-down manner between the range of his waist and shoulders by maintaining a fixed elbow position. The same person agitated each and every vial in a standardized manner to eliminate any variance that might occur with multiple mixers. Each mixing cycle consisted of rapid injection of sterile water into the DS vial, manual agitation for 10 seconds, and a stop period of 3 seconds. The observer continuously inspected the vial, but the 3-second stop period was incorporated to more fully appreciate when we reached our endpoint. After the observer declared the presence of a clear particulate-free solution, an end time was determined by a digital stopwatch and recorded.

Results

We compared the time required to produce a clear, particulate-free DS mixture suitable for IV injection when using warm vs ambient temperature diluent. We made use of SPSS 13.0 (SPSS, Chicago, Ill) for all statistical analysis. The *t* test compares the means of 2 independent populations while ignoring individual differences within each group, so we used this test to compare diluent warmed to 41°C with the diluent at the ambient temperature of the operating room (22°C). We set statistical significance at a *P* value of less then .05. We chose the Levene Test for Equality of Variance to test whether the variation around the independent variable was similar between the warm and ambient temperature groups. We selected the cohen *d* statistic to measure effect size and the magnitude of difference between groups.

Our pilot study results revealed the mean time to achieve a clear particulate-free mixture suitable for IV injection for the warm group vs the ambient temperature group was 1 minute and 21 seconds vs 1 minute and 54 seconds (Table 1). The Levene test indicated that the variance between groups was equal and insignificant. The cohen *d* statistic was 2.46, signifying that the mean time to obtain a clear solution between the groups differed by 2.46 SD, demonstrating a large effect size, relevant to statistical power considerations. Warming the diluent gave way to a large effect on dissolution time (Figure 3). At the conclusion of the pilot study, we decided to revise the observation frequency downward in efforts to further increase effect size and to obtain a more accurate account of dissolution time. Despite the wide interval between observations in the pilot study, we obtained statistically significant results ($P < .005$).

We performed the formal study, based on our experiences with the pilot study, using 16 vials of DS (Table 2). The mean time to dissolve DS with the warm diluent was 58.88 seconds compared with 93.87 seconds for the ambient temperature group ($P < .001$). The Levene test indicated that the variance between groups was equal and insignificant. Increasing the frequency of observation to once every 10 seconds yielded a larger effect size ($d = 4.73$) (Figure 4).

Discussion

Chartrand[9] was the first to make reference to the use of an IV fluid-warming device to facilitate DS reconstitution. By using an IV fluid warmer at 41°C, we demonstrated a favorable reduction in the time required to achieve a clear, particulate-free DS solution suitable for IV injection ($P < .001$). At the first sign of an impending MH crisis, 2.5 mg/kg of IV DS is repeated every 5 minute up to a recommended maximum dose of 10 mg/kg or until symptoms subsides. This translates into a significant mixing burden in an adult patient. For example, in a 72-kg patient, 36 vials of DS are required to reconstitute the maximum recommended dose of 10 mg/kg.

At first inspection, one may liken the idea of supplying an additional heat burden to a patient experiencing an MH crisis to adding fuel to the proverbial fire. Closer analysis reveals the time savings conferred by quickly mixing and administering DS at the onset of MH symptoms will likely more than compensate for the heat burden imposed by the warmed diluent.[1,6] Mitchell and Leighton[7] calculated that an initial 2 mg/kg dose of DS in a 70-kg patient using sterile water warmed to 40°C would fail to generate a net heat gain if one saved 5.1 seconds of mixing time per vial and would create a net heat reduction if more time were saved. Our data suggest a time savings of about 35 seconds per vial when the diluent is warmed to 41°C, translating to a significant net reduction in patent temperature. Precious time saved can be used to attend to other life-saving measures. The time savings afforded by mixing DS with warmed diluent vs ambient temperature sterile water for 1 and 3 mixers is summarized in Table 3.

Neither the DS package insert nor the Malignant Hyperthermia Association of the United States treatment guidelines address the issue of warming the diluent.[6, 10] We were unsuccessful in our efforts to find data specifically about the effectiveness of warmed DS, although anecdotal evidence supports the notion that the drug remains efficacious when warmed. Furthermore, logic dictates that the temperature of an injected drug rapidly equilibrates with patien's temperature.

A comparison of our study with the work of Mitchell and Leighton[7] and Quraishi et al[8] validates the notion that warmed diluent hastens DS solubility, although the methodologies developed to reach this conclusion contrast on several levels. Mitchell and Leighton[7] demonstrated their ability to reconstitute DS in roughly 30 seconds with diluent warmed to 40°C in a single data point study with a small sample. The results of the study by Quraishi et al[8] were similar to those of Mitchell and Leighton[8]; Quraishi et al[8] claimed their data were collected under clinical conditions. Interestingly, they emptied all of their sterile water vials into a sample cup before mixing the DS. This task devours precious time, challenges aseptic technique, and fails to replicate actions that might take place during an MH crisis. They also incorporated warming closets to heat their sterile water. Many of these devices are not intended to warm IV fluids, and we cannot recommend them for use in this application. In addition, neither of the designs in the aforementioned studies incorporated blinding of the observing party.

We endeavored to simulate real-world clinical conditions, revealing a substantial time savings by warming the aqueous diluent to 41°C. We demonstrated that the use of several 1-L bags of preservative-free sterile water run though an IV fluid warming device is an attractive and clinically useful method to rapidly dissolve DS ($P < .001$). Effect size estimates test the strength of a relationship, helping to determine meaningfulness of statistically significant results. The Cohen d statistic for our findings ($d = 4.73$) reveals a large effect size, imparting practical significance to our findings as well. The use of larger sample than used by Mitchell and Leighton[7] and Quraishi et al[8] extended greater strength to our findings. Blinding the observer reduced bias. Limitation to our study included the use of DS 6 months expired and a single manual agitator.

We conducted a pilot study before our study. During the pilot, we incorporated a test trial of several randomly selected DS vial so that we could calibrate the observer's senses to a defined endpoint-an appreciation for the formation of a clear particulate-free solution that would be suitable for IV injection. We based our pilot in part on the work of Mitchell and Leighton[7] by conducting repeated cycles of manual agitation for 30 seconds during continuous observation followed by a 5-second rest to facilitate visual inspection. Although the pilot results suggested a statistically significant difference between the warmed and ambient temperature diluents ($P = .005$), we determined that 30 seconds might have been too long between observations and, in effect, falsely elevated our estimation. We also varied the method of measuring the temperature of the diluent based on our pilot study. We found that withdrawing the warmed diluent from the IV fluid warming device into a syringe led to a time-dependent decrement in the temperature of the diluent. Put another way, the longer we measured the temperature, the greater the decline in the temperature of the warmed diluent. We feared our results would be arbitrarily affected by the diluent after it was withdrawn from the fluid warmer.

Conclusions

Prompt administration of IV DS is the primary determinant of successful treatment of MH. The time needed to mix an appropriate number of DS vials to successfully treat MH necessitates the assistance of multiple providers during a crisis. Warming the DS diluent to 41°C provides a practical method to rapidly solubilize the drug in a period of crisis. In addition, an IV fluid warming device, a reliable and safe tool approved for patient use, is ubiquitous to the operating room environment. Our study was conducted in an operating room environment where we were able to demonstrate a significant reduction in the time from the start of mixing to the ability to administer IV DS.

The Icarus effect was clearly demonstrated, illustrating the important relationship between the effect of temperature and the corresponding state of matter. Warming the equeous diluent hastened the development of a clear and particulate-free DS sodium mixture suitable for IV injection. We should take heed from the physical principle underlying Icarus' misfortune to update our practice and impact patient outcomes in a tremendously positive way. This tragic tale illustrates the vital relationship between the effect of temperature and the state of matter.

Perhaps our research, in addition to the work of Mitchell and Leighton[7] and Quraishi et al,[8] will lay the groundwork for changing MH treatment protocols and ultimately reducing morbidity and mortality.

APPENDIX B

Sample of Text Analysis

Use of heliox for intraoperative bronchospasm: case report

Sentence no.	No of ties	Cohesive item	type	Presupposed item
2	1	bronchospasm	L1	bronchospasm
	2	anesthesia provider	L2	anesthesia emergency
	3	treatment	L1	treatment
	4	negative sequels	L1	disastrous outcomes
3	1	bronchospasm	L1	bronchospasm
	2	general anesthesia	L2	anesthesia provider
4	1	treatment	L1	treatment
	2	bronchospasm	L1	bronchospasm
	3	bronchospasm	L1	bronchospasm
5	1	although	C2	S3
	2	heliox	L1	heliox
	3	used	L1	use
	4	treat	L1	treatment
	5	treatment	L1	treatment
	6	anesthesia practitioners	L1	anesthesia provider
	7	the	L1	treatment
	8	bronchospasm	L1	bronchospasm
	9	patients	L2	bronchospasm
6	1	use	L1	use
	2	heliox	L1	heliox
	3	treatment	L1	treatment
	4	a patient	L2	bronchospasm
	5	bronchospasm	L1	bronchospasm
7	1	bronchospasm	L1	bronchospasm

Anesthetic implications for cancer chemotherapy

Sentence no.	No of ties	Cohesive item	type	Presupposed item
2	1	cancer	L1	cancer
	2	the second most	L2	the most
	3	heart disease	L2	cancer
3	1	cancer	L1	cancer
	2	chemotherapy	L2	cancer
	3	surgery	L2	cancer
	4	radiation	L2	cancer
4	1	chemotherapy	L1	chemotherapy
	2	Systemic cancer therapy	L1	chemotherapy
5	1	Chemotherapeutic agents	L1	chemotherapy
	2	malignant	L1	cell death
6	1	therefore	C3	S5
	2	chemotherapy	L1	chemotherapy
	3	also	C1	S5
	4	healthy organs	L1	normal cell
	5	tissues	L1	normal cell
7	1	in addition	C1	S6
	2	Chemotherapeutic agents	L1	chemotherapy
	3	other	R3	medications
8	1	the effects of chemotherapy	L2	chemotherapeutic agents
	2	treatment	L2	chemotherapeutic agents
9	1	patients	L2	chemotherapy
	2	chemotherapy	L1	chemotherapy

A comparative analysis of isopropyl alcohol and ondansetron in the treatment of postoperative nausea and vomiting from the hospital setting to the home

Sentence no.	No of ties	Cohesive item	type	Presupposed item
2	1	a patient	L2	PONV
	2	the	R2	distressing symptoms
	3	psychological distress	L1	distressing symptoms
	4	physical distress	L1	distressing symptoms
	5	PONV	L1	PONV
	6	surgical experience	L2	surgery
3	1	severe individual patient	L2	PONV
	2	surgical factors	L1	surgery
	3	a patient	L2	PONV
	4	PONV	L1	PONV
4	1	the	R2	severe individual patient factors
	2	Individual patient factors	L1	severe individual patient factors
	3	age	L1	severe individual patient factors
	4	gender	L1	severe individual patient factors
	5	weight	L1	severe individual patient factors
	6	amount of stomach contents	L1	severe individual patient factors
	7	motion sickness	L1	severe individual patient factors
	8	history of nonsmoking	L1	severe individual patient factors

A comparison of preoperative airway assessment techniques: The modified mallampati and the upper lip

Sentence no.	No of ties	Cohesive item	type	Presupposed item
2	1	the	R2	MMT
	2	MMT	L1	MMT
	3	ULBT	L1	ULBT
	4	direct laryngoscopic view	L1	direct laryngoscopic view
	5	MMT	L1	MMT
	6	ULBT	L1	ULBT
3	1	we	R1	the researchers
	2	50patients' airway preoperatively	L2	tracheal intubation
	3	MMT	L1	MMT
	4	ULBT	L1	ULBT
	5	intraoperatively	L2	preoperative anesthesia
	6	laryngoscopic view	L1	direct laryngoscopic view
4	1	descriptive statistic	L2	positive relationship
	2	correlations	L2	positive relationship
5	1	no relationship	L2	positive relationship
	2	MMT	L1	MMT
	3	ULBT	L1	ULBT
	4	Crmack and Lehane scale	L1	Crmack and Lehane scale
6	1	the	R2	ULBT
	2	ULBT	L1	ULBT
	3	the	R2	MMT
	4	MMT	L1	MMT
	5	this study	L1	this study

The Icarus effect: the influence of diluent warming on dantrolene sodium mixing time

Sentence no.	No of ties	Cohesive item	type	Presupposed item
2	1	because	C3	S1
	2	DS	L1	DS
	3	treating	L1	treatment
	4	MS	L1	MS
	5	we	R1	the researchers
3	1	Operating room	L2	MH
	2	we	R1	the researchers
	3	DS vials	L1	DS
	4	warm temperature	L1	Alternative technique
4	1	iv fluid warmer at 41C	L1	warm temperature
	2	Syringe via a t-ways stopcock	L2	DS vials
	3	we	R1	the researchers
	4	the	L1	iv fluid warmer 41C
	5	diluent	L1	iv fluid warmer 41C
	6	Each DS vial	L1	DS vials
5	1	warm diluent	L1	iv fluid warmer 41C
	2	ambient temperature	L1	ambient temperature
	3	hastened	L1	hastening
	4	the reconstruction	L1	the reconstruction
	5	DS	L1	DS

APPENDIX C

A Summary of Halliday and Hasan's Cohesion

A SUMMARY OF HALLIDAY AND HASAN'S COHESION

REFERENCE

1. Pronominals	
(1) singular, masculine	he, him, his
(2) singular, feminine	she, her, hers
(3) singular, neuter	it, its
(4) plural	they, them, their, theirs
1 (1 - 4) functioning as:	
(a) non – possessive, as Head	he/him, she/her, it, they/them
(b) possessive, as Head	his, hers, (its), theirs
(c) possessive, as Deictic	his, her, its, theirs
2. Demonstratives and definite article	
(1) domonstrative, near	this/these, here
(2)domonstrative, far	that/those, there, then
(3) definite article	the
2 (1 - 3) functioning as:	
(a) nominal, Deictic or Head	this/these, that/those, the
(b) place adverbial	here, there
(c) time adverbial	then
3. Comparatives (not complete lists)	
(1) dentity	eg: same, identical
(2) similarity	eg: similar (ly), such
(3) difference (ie: non-identity and dissimilarity)	eg: different, other, else ,additional
(4) comparison, quantity	eg: more, less, as many; ordinals
(5) comparison, quality	eg: as + adjective; comparatives and superlatives

3 (I - 5) functioning as:

(a) Deictic	(1-3)
(b) Numerative	(4)
(c) Epithet	(5)
(d) Adjunct or Submodifier	(1-5)

Note: Not all combinations of (1-5) with (a-d) are possible; the usual functions are those indicated in the last table.

SUBSTITION

1. Nominal substitutes

(1) for noun Head	one/ones
(2) for nominal Complement	the same
(3) for Attributeso	

2. Verbal substitutes

(1) for verb	do, be, have
(2) for process	do the same/likewise
(3) for proposition	do so, be so
(4) verbal reference	do it/that, be it/that

3. Clausal substitutes

(1) positive	so
(2) negative	not

3 (1 - 2) substitute clause functioning as:

(a) reported

(b) conditional

(c) modalized

(d) other

ELLIPSIS

1. Nominal ellipsis

(1) Deictic as Head

i. specific Deictic

ii. non - specific Deictic

iii. Post - deictic

(2) Humerative as Head

i. ordinal

ii. cardinal

iii. indefinite

(3) Epithet as Head

i. superlative

ii. comparative

iii. others

2. Verbal ellipsis

(1) lexical ellipsis ('from right')

i. total (all items omitted except first operator)

ii. partial (lexical verb only omitted)

(2) operator ellipsis ('from left')

i. total (all items omitted except lexical verb)

ii. partial (first operator only omitted)

Note: Where the presupposed verbal group is simple there is no distinction between total and partial ellipsis; such instance are treated as 'total'. Where it is above a certain complexity there are other possibilities intermediate between the total and partial as defined here; such instances are treated as 'partial'.

3. Clausal ellipsis

(1) propositional ellipsis

i. total (all Propositional element omitted)

ii. partial (some Complement or Adjunct present)

(2) modal ellipsis

i. total (all Modal element omitted)

ii. partial (Subject present) [rare]

psis implies propositional ellipsis, and operator ellipsis implies modal
use element other than the Predicator (verbal group) are explicitly

the clause (all elements but one omitted)
H-element Present)
item expressing polarity present)
single clause element present)
e omitted)
ause functioning as:
or answer
answer
nt

nbinations of (I-4) with (1-4) are possible.

items quoted are examples, not complete lists)
nal, (I) = internal.

and, and also
nor, and...not
or, or else

furthermore, add to that
alternatively
by the way, incidentally

that is, in other words
eg, thus

tic (I)

mphatic (I)

tory

Note: Lexical ellipsis implies propositional ellipsis, and operator ellipsis implies modal ellipsis, unless all clause element other than the Predicator (verbal group) are explicitly repudiated.

(3) general ellipsis of the clause (all elements but one omitted)

i. WH- (only WH-element Present)

ii. yes/no (only item expressing polarity present)

iii. other (other single clause element present)

(4) zero (entire clause omitted)

3 (1 - 4) elliptical clause functioning as:

(a) yes /no question or answer

(b) WH - question or answer

(c) 'reported' element

(d) otherwise

Note: Not all combinations of (I-4) with (1-4) are possible.

CONJUNCTION (items quoted are examples, not complete lists)

Note : (E) = external, (I) = internal.

1. Additive

(1) simple : (E/I)

i. additive — and, and also

ii. negative — nor, and...not

iii. alternative — or, or else

(2) complex, emphatic (I)

i. additive — furthermore, add to that

ii. alternative — alternatively

(3) complex, de - emphatic (I) — by the way, incidentally

(4) apposition (I)

i. expository — that is, in other words

ii. exemplificatory — eg, thus

(5) comparison (I)

i. similar	likewise, in the same way
ii. dissimilar	on the other hand, by contrast

2. Adversative

(1) adversative 'proper' : (E/I)	
i. simple	yet, though, only
ii. + 'and'	but
iii. emphatic	however, even so, all the same
(2) contrastive (avowal) : (I)	in (point of) fact, actually
(3) contrastive : (E)	
i. simple	but, and
ii. emphatic	however, conversely, on the other hand
(4) correction : (I)	
i. of meaning	instead, on the contrary, rather
ii. of wording	at least, I mean, or rather
(5) dismissal : (I)	
i. closed	in any/either case
ii. open-ended	in any case, anyhow

3. Causal

(I) general : (E/I)	
i. simple	so, then, therefore
ii. emphatic	consequently
(2) specific : (E/I)	
i. reason	on account of this
ii. result	in consequence
iii. purpose	with this in mind
(3) reversed causal : (I)	for, because
(4) causal, specific : (I)	

i. reason	it follow
ii. result	arising out of this
iii. purpose	to this end
(5) conditional : (E/I)	
i. simple	then
ii. emphatic	in that case, in such an event
iii. generalized	under the circumstances
	iv. reversed polarity otherwise, under other circumstances
(6) respective : (I)	
i. direct	in this respect, here
ii. reversed polarity	otherwise, apart from this, in other respects

4. Temporal

(I) simple : (E)	
i.sequential	then, next
ii.simultaneous	just, then
iii. preceding	before that, hitherto
(2) conclusive : (E)	in the end
(3) correlatives : (E)	
i.sequential	first...then
ii.conclusive	at first/originally/formerly....finally / now
(4) complex : (E)	
i.immediate	at once
ii. interrupted	soon
iii. repetitive	next time
iv. specific	next day
v. durative	meanwhile
vi. terminal	until then

vii. punctiliar	at this moment
(5) internal temporal : (I)	
i.sequential	then, next
ii. conclusive	finally, in conclusion
(6) correlatives : (I)	
i.sequential	first ...next
ii. conclusive	in the first place ...to conclude with
(7) here and now: (I)	
i. past	up to now
ii. present	at this point
iii. future	from now on
(8) summary : (I)	
i. summarizing	to sum up
ii. resumptive	to resume
5. Other ('continuative')	now, of course, well, anyway, surely, after all

6. Intonation

(I) tone

(2) tonicity

IEXICAL

1. Same item

2. Synonym or near synonym (incl hyponym)

3. Superordinate

4. 'General' item

5. Collocation

1 – 5 having reference that is:

(a) identical

(b) inclusive

(c) exclusive

(d) unrelated