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Remimazolam as an Alternative Induction Agent in Monitored Anesthesia Care: An Educational Module

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Remimazolam as an Alternative Induction Agent in Monitored Anesthesia Care: An Educational Module

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They say it takes a village. In dedication to those in mine.

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Abstract

Background: Propofol is a favored intravenous anesthetic; however, studies have shown propofol to have an unstable hemodynamic profile. Currently, myocardial infarction, secondary to intraprocedural hypotension and myocardial ischemia, is the leading cause of postoperative death. Despite its potential for severe adverse effects, propofol remains the leading intravenous anesthetic agent for the induction of general anesthesia and monitored anesthesia care (MAC).

Objective: This project sought to compare the effectiveness and hemodynamic profile of remimazolam and propofol for the induction of anesthesia. Therefore, the primary goal of this Doctor of Nursing Practice (DNP) project was to construct and display an educational quality improvement module for anesthesia providers, educating them regarding the novel drug remimazolam as an alternative to propofol for induction of MAC.

Method: A literature review comparing remimazolam and propofol as induction agents was conducted. With the obtained information, an online educational module was created to present to anesthesia providers. A pre- and post-assessment survey was administered to statistically calculate the knowledge acquired from the educational module. The project was developed and disseminated to Florida International University's Department of Nurse Anesthesiology alumni using an online platform that broadcasted the module, provided anonymity for the surveyors, and provided unbiased data collection.

Results: The project established predetermined benchmarks to assess success and quantify knowledge acquisition through the educational module. Specifically, a 20% increase in the average of correct answers from the pre- to post-assessment or an overall average of 85% in the post-assessment was considered indicative of project success. The analysis revealed that the average percentage of correct responses on the pre-assessment survey was 63.6%, while the post-assessment survey yielded an average of 85.5% correct responses. These findings demonstrate a substantial increase in knowledge of 21.9% following participants' exposure to the educational module.

Discussion: The project demonstrated its efficacy in meeting the established benchmarks by analyzing both the pre- and post-assessment surveys. The discernible enhancement in learning outcomes attests to the favorable influence of the educational intervention, significantly improving participants' comprehension of the subject matter.

Conclusion: The educational module implemented in this project yielded significant improvements in the knowledge and attitudes of anesthesia providers regarding the utilization of remimazolam as an alternative to propofol for the induction of MAC. By disseminating knowledge about remimazolam and its potential benefits, this project contributes to advancing evidence-based practice and enhancing patient care during the induction of monitored anesthesia care.

Keywords: Remimazolam, propofol, hemodynamic effects, perioperative, induction, anesthesia, mortality, morbidity, sedation, monitored anesthesia care, MAC, hypotension, cardiac, mean arterial pressure

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Introduction

Problem Identification

There have been many medical advancements throughout the last decade; however, there has only been a slight improvement in the rates of 30-day postoperative mortality. While most patients fear intraoperative anesthesia-related death, postoperative mortality is approximately 1000 times more common, with myocardial infarction (MI) being the leading cause.[1] Studies have shown a formidable relationship between mortality and perioperative hypotension, which can lead to myocardial and kidney injury.[1]

During induction of anesthesia, there is an increased risk of hemodynamic instability, arrhythmias, and hypoxia.[2] Approximately a third of all intraoperative hypotension (IOH) transpires during the induction of anesthesia.[1] Therefore, this process is critically significant, especially in compromised patients. Post-induction hypotension has primarily been attributed to the patient's medical history and anesthetic management, which the anesthesia provider can significantly modify.[1] By avoiding perioperative hypotension, the anesthesia provider, in turn, decreases the patient's risk of postoperative complications, such as MI, and therefore reduces postoperative mortality rates.

To date, there is no ideal inducing agent available. The choice of anesthetic agents for induction of anesthesia largely depends on factors such as the pathophysiological condition of the patient, the type of surgery, the anesthesia providers' personal experience, or institutional policy.[2,3] Although it has been considerably associated with post-induction hypotension, propofol is the leading intravenous anesthetic for general anesthesia and monitored anesthesia care (MAC).[4]

Propofol's popularity is attributable to its depression of upper airway reflexes, mild bronchodilation, and amnestic and sedative properties. Conversely, propofol may also cause adverse reactions such as pain on injection, respiratory depression, thrombophlebitis, and cardiovascular depression producing hemodynamic instability.[2]

Background

The anesthesia provider's goal is always to control the patient's hemodynamic status. Recent studies determined hypotension safety thresholds to be narrow, with even brief periods of minor hypotension linked to myocardial injury, renal injury, and increased mortality. Sessler et al. found the risk of postoperative mortality is markedly increased when mean arterial pressure (MAP) of 70mmHg or less was maintained for just 10 minutes (min).[1] Myocardial injury threshold was deemed at approximately 65mmHg, while renal injury was associated with a MAP threshold of approximately 75mmHg. Similarly, the MAP threshold regarded as harmful during general surgery was approximately 65mmHg.[1,5] Disturbingly, many of these hypotensive states are still routinely tolerated by many anesthesia providers.[1]

Propofol is a favored intravenous anesthetic with a quick onset of action and a short half-life.[6] Nevertheless, studies have shown propofol to yield a substantial decrease in systolic, diastolic, and mean arterial (MAP) pressures.[7] Clinically, a decline in arterial pressure reduces cardiac output, which may cause myocardial ischemia, postoperative organ failure, and even death.[5-7] In addition to the effects on arterial pressure, propofol has been demonstrated to significantly reduce systemic vascular resistance. A recent study by Saugel et al.[5] resulted in a 25% reduction in systemic vascular resistance index, which they concluded was the primary cause for a third of their patients having a MAP of < 65mmHg, after propofol administration.[5]

Propofol's cardiovascular depressing ability has been credited to multiple causes, such as its effects on peripheral resistance leading to a reduction in preload. Other contributing reasons may be reducing the baroreceptor response to blood pressure, which inhibits compensatory tachycardia or reducing arterial pressures affecting afterload.[6] While multiple studies have concluded various causes, there is no question regarding its overall ability to precede hemodynamic instability.

Comparable cardiovascular depression has also been observed in patients with ischemic and valvular heart disease (VHD) during induction with propofol. Several patients with VHD suffer from various underlying disorders and cardiac dysfunction. Therefore, hemodynamic stability during anesthesia induction is of the utmost importance. This is also true for patients with coronary artery disease (CAD). The detrimental effects of anesthetic agents in patients bearing CAD, especially those with compromised ventricular function, have been well documented.[7-9]

In the arena of cardiovascular surgery, propofol is widely used for inducing sedation in procedures such as transesophageal echocardiography, endocardial cardioversion, transthoracic electrical cardioversion, and other various cardiac procedures.[5] Hemodynamic stability is critical during cardiac interventional procedures, as there are multiple degrees of cardiac dysfunction and hemodynamic fluctuations.[10] In addition, cardiac patients have poor cardiovascular reserve function, rendering it demanding to tolerate the effects of anesthetics, such as propofol, on circulatory function.[10] With cardiac procedures being related to high incidences of postoperative complications and patient mortality,[11] anesthesia providers must be well-versed regarding the effects of anesthetic drugs such as propofol on perioperative hypotension and its implications for postoperative mortality.

Maintaining stable hemodynamics in the perioperative period while performing general anesthesia or MAC is essential. MAC is a mode of anesthesia care in which the patient is sedated but can breathe spontaneously without mechanical ventilation. In the U.S., nearly one-third of ambulatory anesthesia services for therapeutic or diagnostic procedures are performed under MAC.[12] Similar medications are used during the MAC induction process compared to general anesthesia. However, they are administered in lower doses to achieve conscious sedation. Propofol, for example, is usually administered at a rate between 30 and 180 μg/kg/min.[12] Studies have shown this rate may still cause hemodynamic instability, such as hypotension, and even lead to respiratory depression.[12] Therefore, electing the appropriate anesthetic induction agent for any type of procedure is the key to reducing organ injuries and improving patient prognosis.

Scope of the Problem

A study by Walsh et al. examined the data of 33,330 noncardiac surgical patients to investigate an association between intraoperative MAP, from less than 55-75mmHg, and postoperative myocardial injury and acute kidney injury (AKI).[13] The authors found that patients who experienced a hypotensive state of a MAP of 55mmHg or less had an approximately 1.5-fold higher risk of myocardial injury or AKI than those who did not have hypotension post-induction.[13] Additionally, the study found nearly a two-fold increased risk for cardiac complications in hypotensive patients.[13]

A quarter of all mortality is credited to myocardial ischemia, far exceeding sepsis (9%) and bleeding (14%). According to the American Heart Association, MI is the third-leading cause of death, which includes 4% of surgical inpatients over the age of 45 years. Approximately 4% of patients who suffer postoperative complications secondary to myocardial ischemia die within the month of surgery, with more than 90% of MI cases occurring 2 days after surgery.[1]

Consequences of the Problem

A recent study investigated the associated increase in postoperative healthcare resource utilization (HRU) with perioperative hypotension. Of the 42,800 examined patients undergoing non-cardiac surgeries, 37.5% experienced hypotension after induction.[14] These patients were found to have an extended hospital stay of 4.32 hours/patient.[14] With approximately 27 million people undergoing non-cardiac surgeries in the U.S. annually, 10 million of these patients may experience hypotension after induction. Considering the average cost of 1 hospital day is over a thousand dollars, preventing hypotension during induction would yield sizeable savings for the U.S. health system. [14]

Compared to normotensive patients, this study also revealed a higher chance of being discharged to a care facility (22.1% vs. 18.1%) or readmitted within 30 days of discharge (6.2% vs. 5.0%) for patients who experienced hypotension perioperatively. Readmissions are a fundamental quality metric for healthcare institutions, as they may acquire reimbursement penalty losses[15] and symbolize an approximate $50.7 billion economic burden to the U.S. health system.[16] Another study went a step further by quantifying the correlation between improved intraoperative hypotension in a hospital whose annual volume is 10,000 non-cardiac surgical patients and cost savings.[17] The authors concluded a savings ranging from $1.2 to $4.6 million per year if blood pressures were maintained at a MAP>65mmHg perioperatively.[17]

Knowledge Gaps

A fundamental knowledge gap that continually perpetuates this problem is that there is no clear or widely accepted definition of intraoperative hypotension. Hypotension is commonly described using absolute or relative thresholds for different blood pressure components compared to baseline.[18] The duration of exposure to hypotension and its possible implications are

also vague. Bijker et al. conducted a systematic review that identified 140 definitions for perioperative hypotension in 130 articles.[18] Hypotension was characterized by either MAP, systolic blood pressure, or a combination of both, allowing for either threshold relative to baseline or absolute thresholds. The most customary description of hypotension was a 20% diminution of systolic blood pressure from baseline.[18] The authors found a 93% incidence of intraoperative hypotension for greater or equal to 1 minute when using this standard definition. Similarly, the researchers discovered an 88% exposure to hypotension of greater or equal to 5 minutes and a 78% occurrence of hypotension that lasted 10 minutes or more when considering a 20% reduction in systolic blood pressure.[18] When using an absolute MAP threshold of 65mmHg, the results generated a 65% prevalence for an exposure equal to or greater than 1 minute, 49% for exposures lasting 5 minutes or more, and 31% incidence for hypotension lasting greater than or equal to 10 minutes.[18]

IOH is common in patients receiving anesthesia for induction. As mentioned previously, IOH has been associated with postoperative complications such as acute kidney injury, myocardial injury, and even death. Therefore, IOH may be an important modifiable risk factor for postoperative complications. However, the ideal therapeutic method for IOH remains indefinable. Additional research is required to define specific hypotensive thresholds to create therapeutic strategies to treat and avoid IOH. In the interim, anesthesia providers must stay up to date with the latest research, evidence-based practices, and contemporary anesthetic agents to prevent IOH and mitigate its adverse effects.

Proposal Solution

Since its clinical debut in 1986, propofol has been considered the “ideal” intravenous hypnotic agent. Nevertheless, clinicians and scientists have questioned whether propofol’s

adverse effects are worth the benefits. While propofol has a fast onset of 9 to 51 seconds and a recovery time of approximately 10 minutes, it possesses an unattractive safety profile.[19] For example, one of propofol's most reported adverse effects is pain through intravenous administration. Additionally, its lipid formulation presents a risk of bacterial contamination from open air, aside from its well-documented risk of cardiorespiratory depression.[19]

In July 2020, the Food and Drug Administration (FDA) approved a new benzodiazepine intravenous medication for sedation. Remimazolam directly interacts, via polysynaptic pathway inhibition, with gamma-aminobutyric acid (GABA) and modifiable chloride channels. This interaction inhibits neural activity through an increase in chloride influx.[19] Remimazolam displays a promising combination of advantages of midazolam and propofol, 2 of the most commonly used anesthesia intravenous sedatives. Remimazolam exhibits a fast onset of action, a short recovery time, and a good safety profile.[19] During the 2 years since its public release, remimazolam has been utilized in several clinical settings, such as sedation for outpatient procedures, minor examinations, and even for the induction and maintenance of general anesthesia. The novel medication aims to be significantly beneficial for patient populations such as the elderly, the critically ill, hemodynamically unstable patients, and those patients with liver and kidney insufficiency.[19]

Recent studies have shown that remimazolam has fewer cardio-depressant effects during induction of anesthesia with a significantly lower rate of hypotension when compared to propofol.[4] In addition, remimazolam is quickly hydrolyzed to an inactive metabolite (CNS 7054) by non-specific tissue esterase activity, which is responsible for its fast onset and offset of sedation and its predictable duration of action.[19] Similarly to other benzodiazepines, flumazenil can be administered to reverse remimazolam's sedative effects.[19] Due to its promising properties,

remimazolam seems to have numerous advantages over currently popular sedative drugs. Therefore, the author proposes to investigate if, in interventional cardiovascular patients receiving monitored anesthesia care, the use of remimazolam versus propofol decreases hemodynamic instability and reduces the risk of mortality and morbidity.

Literature Review

Search Strategy

The methodology implemented aimed to obtain evidence-based research concerning the hemodynamic effects and consequent mortality rates of propofol and remimazolam. The search strategy entailed consecutive series of primary research studies that collected qualitative data. The retrieval and usage of electronic data-based sources were essential to the execution of this research. The present research appraisal included succeeding and peer-reviewed relevant studies through established platforms such as the Cumulative Index of Nursing and Allied Health Literature (CINAHL), Medline, and EMBASE. Propofol has been extensively researched since its introduction in the 1980s. Therefore, advanced search characteristics were publication dates between 1982 and 2022, peer-reviewed journals, full text, and written in English.

The research's inclusion and exclusion criteria focused on headings, including related combinations of MeSH terms, truncated phrases, key phrases, and Boolean logic. Keywords searched were: "remimazolam," "propofol," "hemodynamic effects," "perioperative," "induction," "anesthesia," "mortality," "morbidity," sedation," "monitored anesthesia care," "MAC," "hypotension," "cardiac," and "mean arterial pressure."

An additional search was performed by employing an ancestry approach, which allowed the examination of theoretically pertinent data by investigating articles cited by other relevant

studies. The recovered publications were assessed for applicability by implementing inclusion and exclusion criteria and reviewing the title and abstract of each.

The search retrieved a considerable number of publications totaling 130 articles. Further screening led to the exclusion of 118 publications for using primary research methodologies such as systematic reviews, observational studies, case reports, preliminary clinical trials, or unrelated or inapplicable implementation strategies. Further studies were excluded due to duplicate citations and those performed on pediatric patients younger than 18 years of age.

Study Characteristics

Through literature review, hemodynamic data was obtained from 9 Level I experimental, randomized controlled trials (RCT)[8-10,20-25], and 1 Level II quasi-experimental trial.[26] These trials sought to compare either propofol, remimazolam, or both in a multitude of settings during the induction of anesthesia to analyze various aspects of the medications including hemodynamics. This data was used to ascertain a hemodynamic comparison between the 2 medications to associate these drugs.

Literature Review Table

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Chae et al.,[20] 2022	-Level 1: Experimental, Randomized control trial (RCT) -The study was a double blinded, randomized, single center, 6-arm study. -The authors randomly allocated 120 patients undergoing general anesthesia into 6 dose groups of induced by bolus intravenous (iv) remimazolam. Their goal was to investigate the bolus dose needed for loss of consciousness (LoC). Respiratory depression (RD), LoC, patient state index (PSI), and hemodynamic variables were evaluated during this time.	Inclusion Criteria: -ASA I-III -Greater than 18 years of age -Undergoing elective surgery under general anesthesia Exclusion Criteria: -Patients undergoing hepatectomy -Liver transplant patients or history of liver disease -Kidney disease -Uncontrolled hypertension -Diabetes -Intolerance or hypersensitivity to benzodiazepine -History of drug addiction -Glaucoma -Heart failure -Peripheral artery disease -Chronic obstructive lung disease -Pregnancy -Patients undergoing regional anesthesia before anesthetic induction Enrollment -Assessed for eligibility (*n* = 135) -Excluded (*n* = 11) -Randomized (*n* = 120) -Allocation: • Group 1 0.02mg/kg (*n* = 20) • Group2 0.07mg/kg (*n* = 20) • Group 3 0.12mg/kg (*n* = 20)	-Independent variable 1 (IV1): Remimazolam at 0.02mg/kg -Independent variable 2 (IV2): Remimazolam at 0.07mg/kg -Independent variable 3 (IV3): Remimazolam at 0.12mg/kg -Independent variable 4 (IV4): Remimazolam at 0.17mg/kg -Independent variable 5 (IV5): Remimazolam at 0.22mg/kg -Independent variable 6 (IV6): Remimazolam at 0.27mg/kg -Dependent variable 1 (DV1): LoC -Dependent variable 2 (DV2): RD -Dependent variable 3 (DV3): PSI -Dependent variable 4 (DV4): MAP Dependent variable 5 (DV%): HR	Methods used to answer the question: -Randomization of patient placement was achieved using R Statistical Software based on the closed envelope method. -Patient was placed on standard monitoring systems and the depth of anesthesia was assessed using a PSI measure with a Sedline brain function monitor. -Patients were administered their group designated dose and hemodynamic variables and PSI were evaluated every 30 seconds for the first 5 minutes during anesthesia induction. -LoC was evaluated every 10 seconds from the point of induction agent administration. -Signs of RD were observed continuously from start of induction. -Statistical analysis for the intergroup differences were obtained using one-way analysis of variance or Kruskal-Wallis test for continuous or ordinal variables and Fisher's exact test or X^2 test for categorical variables. -*P*-value <0.05 was deemed statistically significant. -Dose-response model of time of LoC and RD was founded on the parametric time-to-event models	Time to LoC (%RSE): • Emax= 0.023 [s^{-1}] (10.1) • ED50 (mg/kg) =0.11(10.5) • ED95 (mg/kg) = 0.19 • Hill coefficient(g)= 5.3(24.9) • Coefficientofageon ED50= -0.014 (26.4) Time to RD (%RSE) • Emax= 0.018 [s^{-1}] (19.2) • ED50 (mg/kg) =0.14(25.9) • ED95 (mg/kg) = 0.27 • Hill coefficient(g)= 4.6(12.8) • Coefficientofageon ED50= -0.013 (27.9) **Patient state index (%RSE)** • Emax= 58.1 [%] (5.5) • ED50 (mg/kg) =0.12(10.3) • ED95 (mg/kg) = 0.68 • Hill coefficient(g)= 1.7(11.1) • Coefficientofageon ED50= -- **Mean arterial pressure (%RSE)** • Emax= 27.77 [%] (12.48)	The findings revealed that a dose of 0.11mg/kg would be needed to safely induce 50% of the general population (ED50), while a dose of 0.19mg/kg was necessary for an ED95. -The dose related to RD in ED50 was found to be 0.14mg/kg and 0.27mg/kg for ED95. -The results showed a significant correlation between the older age and lower ED50 and ED95 endpoints. -ED50/ED95 and the Hill coefficient of PSI decline was 0.12/0.68mg/kg and 1.7, respectively. -A maximum decrease in MAP of 27.8% was seen with an ED 50 of 0.14mg/kg	-The authors concluded that an IV bolus of remimazolam at a dose of 0.19mg/kg is needed to induce loss of consciousness in 95% of patients aged 60 years with a sufficient safety margin between LoC and RD throughout all age groups. Furthermore, the study concluded that remimazolam could be safely employed without producing substantial hemodynamic instability. -The authors recommended adapting the dose to the patient's age based on the results proving a substantial age-ED50 correlation.	-The RCT is rated a Level I- High Quality of Evidence based on the John Hopkins Level of Evidence Table. -Authors state they have no conflict of interest. Limitations: -The study population contained primarily older patients with co-morbidities that may affect hemo-dynamic values. Consequent-ly, the results regarding hemo-dynamic variables should be interpreted with this in mind.

		• Group 4 0.17mg/kg (*n* = 20) • Group 5 0.0.22mg/kg (*n* = 20) • Group 6 0.27mg/kg (*n* = 20) -Analyzed (*n* = 120) - The study took place in Yonsei University Gangnam Severance hospital in Seoul, Korea, May 2021 to July 2021.	-LoC was defined as unresponsiveness to mild shaking of the patient's shoulder. -RD was defined as the cessation of spontaneous breathing and warranting assisted ventilation. -Primary endpoints were defined as the ED50 and ED95 of IV bolus administration of remimazolam for LoC. -Secondary endpoints were to evaluate the dose-response relationships regarding PSI, RD, and hemodynamic points.	assuming constant, Weibull, and log-logistic hazard functions. -PSI analysis was obtained by evaluating the effect compartment model, turnover, model, and turnover model coupled to upstream transit compartments. -Models were employed using NONMEN 7.4.	• ED50 (mg/kg) =0.1369(28.94) • ED95 (mg/kg) = 2.60 • Hill coefficient(g)= 1 • Coefficientofageon ED50= --	and an ED95 of 2.60mg/kg.		Another limitation was the lack of evaluating the synergistic effect anesthetic induction agents have with benzodia-zepine in which may have affected the time to LoC, RD, and hemo-dynamic variables.

Pharmacodynamic parameters of efficacy and safety endpoints. Values in parentheses are percentages. ED50, 50% effective dose; ED95, 95% effective dose; LoC, loss of consciousness; RD, respiratory depression; %RSE, percent relative standard error.

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Liu et al.,[9] 2021	-Level 1: Experimental, Randomized control trial (RCT) -Double blinded study: Participants, data collectors, and data analysts were blinded to group allocations. -Patients undergoing cardiac surgeries were randomly administered either remimazolam or propofol during induction of their general anesthesia. The patients' hemodynamics during the induction process were then compared and evaluated.	-Patients that were scheduled for MVR/AVR/DVR on CPB who were between the ages of 35-65 years old that had a cardiac function graded as class II or III by the New York Heart Association and an ASA III were included. -Assessed for eligibility: *n* = 60 -Excluded: *n* = 0 -Randomized: *n* = 60 -Allocation: • Group Remimazolam: *n* = 30 • Group Propofol: *n* = 30 -Attrition rate: *n* = 0 The study was conducted at the Department of Anesthesiology located in The First Affiliated Hospital of Guangxi Medical University in Nanning, China between December 2020 and February 2021.	-Independent variable 1 (IV1): Remimazolam -Independent variable 2 (IV2): Propofol -Dependent variable 1 (DV1): Change in heart rate (beat/min) -Dependent variable 2 (DV2): Change in MAP (mmHg) -Dependent variable 3 (DV3): Hypotension (MAP <60mmHg) -Dependent variable 4 (DV4): Norepinephrine use (50 ug)	Methods used to answer the question: -Outcome measures for HR and MAP were collected by recording their value at baseline, 3 minutes after induction, directly prior to intubation (10 minutes after induction), 1 minute after intubation, and 5 minutes after intubation. The change in both HR and MAP was the difference between their corresponding maximums and minimums to baseline. -IBM SPSS Statistics version 25 was implemented to examine the normality of the collected data by the Kolmogorov-Smirnov test. -The normally distributed data were conveyed as the mean ± SD and were evaluated between the groups using the student's unpaired *t*-test. Nonparametric data were analyzed by the x^2 test or Fisher's exact test for intergroup differences. $p < .05$ was the value used to define statistical significance. -The sample size was calculated based on a pilot study. In this pilot study, the mean ± SD ▲MAP in the remimazolam group and the propofol group was 16.8 ± 7.2 mmHg and 23.6 ± 9.1 mmHg, respectively. For a difference in the 20% reduction of ▲HR and ▲MAP at a significance level of 0.05 (2-sided) and power of 0.9, we required a minimum of 25 patients in each group.	Remimazolam group: -▲HR (beat/minute) = 9.3 ± 9.9 -▲MAP (mmHg)= 19.5 ± 7.5 -Hypotension, n (%) = 5(16.7%) -Norepinephrine (ug)= 8.3 ± 18.9 Propofol group: -▲HR (beat/minute) = 6.5 ± 8.4 -▲MAP (mmHg)= 26.7 ± 9.1 -Hypotension, n (%) =13 (43.3%) -Norepinephrine (ug)= 33.3 ± 42.2 *p*-value: -▲HR (beat/minute) = .2380 -▲MAP (mmHg)= .0016 -Hypotension, n (%) = .0242 -Norepinephrine (ug)= .012	Primary Outcomes: -The change in MAP was considerably higher in the propofol group when compared to the remimazolam group throughout induction. -The occurrence of hypotension and the average use of norepinephrine during induction was lower in the remimazolam group than the propofol group. -No substantial difference was found within changes in heartbeat when both groups were compared.	Remimazolam demonstrated to be effective and safe upon induction of general anesthesia and may be used as an alternative to propofol for patients undergoing valve replacement surgery.	-The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. -While conclusions were favorable towards remima-zolam, further studies ought to be performed with a larger sample size and age range to better appraise the risk/benefits of remimazolam in patients undergoing valve replacement.

Abbreviations: ▲HR, maximum change of heart rate; ▲MAP, maximum change of mean arterial pressure.

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Doi et al.,[21] 2020	-Level 1: Experimental, Randomized control trial (RCT) -Study was a multicenter, randomized, single-blind, parallel group study. -Patients were randomly chosen to receive either remimazolam or propofol to allocate them in 1 of 2 groups. While the allocation of the amount of dosing (either 6mg/kg/h or 12mg/kg/h) for the remimazolam group was determined using a double-blinded technique. -Once patients were allocated to their corresponding groups the efficacy and safety of remimazolam compared with propofol for induction of general anesthesia was evaluated.	Inclusion Criteria: -20 years old or older -Body weight of 100kg or less -undergoing elective surgery requiring general anesthesia with tracheal intubation -Surgery would require a hospitalization stay of 3 days or greater. -Patient was assigned an ASA of I or II by the standards of the American Society of Anesthesiologists physical status criteria. Randomized Patients: *n* = 391 -Group 1: Remimazolam (6ml/kg/h): *n* = 158 • Intervention Received *n* = 150 • Discontinued study *n* = 5 • Patient withdrawn by PI *n* = 2 • Met exclusion criteria *n* = 1 • Analyzed *n* = 150 • Violations of Protocol *n* = 12 • Completed *n* = 138 -Group 2: Remimazolam (12mg/kg/h): *n* = 156 • Intervention Received *n* = 156 • Discontinued study *n* = 4 • Patient withdrawn by PI *n* = 1 • Met exclusion criteria *n* = 1 • Analyzed *n* = 150	-Independent variable 1 (IV1): Remimazolam at 6mg/kg/h -Independent variable 2 (IV2): Remimazolam at 12mg/kg/h -Independent variable 3 (IV3): Propofol The determination of induction efficacy, also stated as primary endpoint, was determined by the absence of the following variables: -Dependent variable 1 (DV1): Signs of Intraoperative awakening as defined by change in BP or HR, sweating, or lacrimation. -Dependent variable 2 (DV2): The use of rescue sedation. -Dependent variable 3 (DV3): Intraoperative recall -Dependent variable 4 (DV4): Body movement	Methods used to answer research question: -Patients were induced for general anesthesia with the investigational medication combined with Remifentanil at 0.25 and 0.5 ug/kg/min and Rocuronium for muscular paralysis. Groups 1 and 2 were induced via a continuous infusion of 6 or 12mg/kg/h (respectively) for up to 2.5 minutes. Group 3 was induced with the use of a 2.0-2.5mg/kg bolus of Propofol infused over 1 minute. - The investigative medication was discontinued if LoC was not achieved within 2.5 minute and a rescue sedative was administered. -When signs of intraoperative awakening were noted and required urgent action for Group 1 or 2 a rapid infusion of remimazolam at a rate up to 12mg/kg/h was given for 1 minute. If signs continued the infusion was discontinued and a rescue sedative was administered. Group 3 was allowed to adjust infusion rate appropriately and was discontinued and replaced by a rescue sedative if signs of awakening continued. -Body movements were observed and documented from moment of LoC until the end of	Primary endpoint: *n* (%) -Group 1: 150 (100.0) -Group 2: 150 (100.0) -Group 3: 75 (100.0) Differences (97.5% CI) [*p*-value]: -Group 1 vs Group 3 and Group 2 vs Group 3: 0.0 (−, −) (−0.0628; 0.0324) (−0.0628; 0.0324) Non-inferiority of remimazolam -95% confidence interval (− 0.0487; 0.0250)	Efficacy of all 3 groups as successful induction medications was found to be 100%. There were no occurrences of body movements, necessity for the use of rescue medications, and no indications of intraoperative arousal or recall. Remimazolam was demonstrated to be a non-inferior induction medication when compared to propofol. Secondary Endpoints: -The time to LoC was longer in both remimazolam groups when compared to propofol. The incidence of adverse reactions was overall higher in the propofol group when compared to remimazolam	The clinical trial validated that remimazolam is a non-inferior medication to propofol regarding its efficacy as a sedative hypnotic for the induction of general anesthesia.	-The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. -A possible limitation to the study includes the fact that the trial was unable to fully blind the investigators, and therefore, a theoretical bias may be declared. Another limitation is the limited experience with remimazolam. Therefore, the time intervals during recovery must be considered with some caution and may not yet represent the full spectrum of its abilities or use.

		• Violations of Protocol *n* = 16 • Completed *n* = 134 -Group 3: Propofol: *n* = 77 • Intervention Received *n* = 75 • Discontinued study *n* = 2 • Analyzed *n* = 75 • Violations of Protocol *n* = 5 • Completed *n* = 70 The study was performed at 49 Japanese sites between November 2012 and March 2013.		surgery and distinguished between voluntary/purposeful and involuntary/bucking movements. -Intraoperative recall was assessed using documented intraoperative BIS scores and the Brice Questionnaire. The questionnaire was administered within 24 hours after the surgery and prior to the patient being discharged from recovery. Measurement Scales: -Full Analysis Set (FAS) was used to perform the primary efficacy/primary endpoint analysis. -Safety analysis was conducted with the Safety Set (SAF). -The Wilson method was used to calculate efficacy rates with a 2-sided 97.5% confidence intervals (CIs). -Non-inferiority was defined as having a CI with a lower limit of more than − 10%. -The Chi square test was implemented for statistical comparison. -The Newcombe-Wilson hybrid score without continuity correction was used in the occurrence of any 100% efficacy rate. This would estimate the 95% CI for the difference between groups.		groups. Hypotension was significantly higher in the propofol group when compared to the remimazolam groups. Injection site pain was reported in 18.7% of propofol patients but not in those receiving remimazolam.		-Some of the study's strengths is the applicability to daily practice as the primary endpoint consists of combinations of factors that are extremely relevant to clinicians. Clinical parameters, such as heart rate and BP, assess the effectiveness routine use of anesthetics.

FAS Full Analysis Set, PI Principal Investigator

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Dai et al.,[22] 2021	-Level 1: Experimental, Randomized control trial (RCT) -Patients scheduled for elective surgery were randomly selected for placement in 1 of 4 groups. All patients received a single shot of an induction agent during induction for general anesthesia. -The goal of the study was to evaluate the safety and efficacy of the medications as anesthetic agents during the induction period for general anesthesia.	Inclusion Criteria: -Between ages of 18 and 65 years old -ASA rating of Class I or II -18kg/m^2<BMI<30kg/m^2 -undergoing elective surgery Randomized Patients *n* = 190 -R1 group (0.2mg/kg): *n* = 46 • Received intervention *n* = 46 • Analysis *n* = 46 -R2 group (0.3mg/kg): *n* = 51 • Received intervention *n* = 51 • Analysis *n* = 51 -R3 group (0.4mg/kg): *n* = 45 • Received intervention *n* = 45 • Analysis *n* = 44 • Protocol violation *n* = 1 -P group (Propofol group): *n* = 48 • Received intervention *n* = 48 • Analysis *n* = 48	-Independent variable 1 (IV1): Remimazolam at 6mg/kg/h -Independent variable 2 (IV2): Remimazolam at 12mg/kg/h -Independent variable 3 (IV3): Propofol at 2mg/kg -The study sought to demonstrate the efficacy and safety of remimazolam when compared to propofol during the induction of general anesthesia. -The primary efficacy endpoint was defined as meeting the following dependent variables: • Dependent Variable 1 (DV1): Successful induction of anesthesia without recall. • Dependent Variable 2 (DV2): The absence of rescue sedation	Methods used to answer research question: -Patients were randomized by the random digit table. -Doses of each medication pertinent to their assigned group were given through IV administration of ≤1 minute. -A Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale was implemented to assess sedation levels -Supplemental doses of 0.05mg/kg remimazolam or 0.5mg/kg propofol respectively were administered if loss of consciousness was not achieved within 1 minute. -IV Sufentanil of 0.3-0.5 μg/kg was given a minute before the induction. -Once induction was successful, Cisatracurium 0.15-0.2 mg/ kg was immediately administered for tracheal intubation.	Successful induction rates: -R1= 89% -R2= 94% -R3= 100% -P= 100% Rescue Sedation: -R1= 11% -R2= 6% -R3= 0% -R4=0% Adverse effects: -Injection site pain: • R1= 0% • R2= 0% • R3= 0 % • P = 27% -Hypotension • R1 = 13% • R2= 24% • R3= 34% • P= 44% GPower was used to estimate that 158 patients in total would provide 90% power at a 0.05 significant level.	Higher induction rates were found with higher doses of remimazolam. Remimazolam at a dose of 0.3-0.4mg/kg demonstrated to be comparable to propofol induction rates ($p > 0.05$) At a lower dose of 0.2mg/kg, remimazolam had an induction success rate of 89% with the need of additional rescue medication. R1 induction rate is lower than *p* group ($p < 0.05$). Upon induction, hypotension was found to be lower in R1 and R2 group when compared to *p* group. Meanwhile, there was no significant difference between R3 and *p* group ($p \geq 0.05$). The study found that higher doses of remimazolam did increase hypotension rates.	The clinical trial concluded that remimazolam administered at high concentrations had an equivalent efficacy for induction as propofol. The study showed that remimazolam is a safe and effective induction drug with less adverse effects for general anesthesia in ASA I and II patients.	The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. The studies methods and application for remimazolam to be used as a safe and efficacious medication during induction is feasible and highlighted to be 1 of the trial's strengths. However, a limitation was noted for the lack of use of remimazolam as anesthesia maintenance. Further studies are needed to evaluate its efficacy and safety in the maintenance of general anesthesia. A limitation of this study was the failure to include patients categorized as ASA III. Therefore, these results may not be applied to high-risk patients.

			with other sedatives • Dependent Variable 3 (DV3): The lack of additional dosages of either remimazolam or propofol during the induction period -Safety endpoint was established by the absence of adverse effects during induction.	Measurement Scales: -A Power Analysis was performed using GPower (version 3.1.9.2) to establish a 0.05 significance level. -Data was analyzed by implementing the SPSS version 20.0 statistical software. -The SD expressed the distributed measurement data. Values less than <0.05 was considered a significant statistical difference. -Measurements among groups were compared using the 1-way ANOVA.		There were no incidences of injection site pain observed for the remimazolam groups while the *P* group had a 27% incidence rate ($p < 0.01$). No serious adverse reactions were found during induction.		

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Doi et al.,[23] 2020	- Level 1: Experimental, Randomized control trial (RCT) -The study is a multicenter, randomized, double-blind, parallel group trial whose goal is to determine the safety and efficacy of remimazolam for induction of general anesthesia in high-risk surgical patients. -A dynamic allocation was performed to randomly chose patients for both groups. Group A would be induced using 6mg/kg/hour of remimazolam. Group B would be induced by 12mg/kg/hour u of remimazolam. Both groups would receive induction dose until LoC. -Remimazolam was also infused up to 2mg/kg/hour for maintenance of anesthesia in both groups.	Inclusion Criteria: -ASA III or higher surgical patients undergoing general anesthesia -All patients are planned to be tracheal intubated and expected to be hospitalized for at least 3 days after surgery. -Patient over the age of 20 -Patients with bodyweight of ≤ 100 kg Randomized Patients: *n* = 67 -Group A: Remimazolam (6ml/kg/h): *n* = 33 • Patient Withdrew Consent *n* = 2 • Safety Analysis Set (SAF) *n* = 31 • Full Analysis Set (FAS) *n* = 31 • Violations of Protocol *n* = 4 • Per Protocol Set (PPS) = 27 -Group B: Remimazolam (12mg/kg/h): *n* = 34 • Patient withdrawn secondary to patient safety *n* = 2	-Independent variable 1 (IV1): Remimazolam at 6mg/kg/hour -Independent variable 2 (IV2): Remimazolam at 12mg/kg/hour -The primary efficacy endpoint for the functional anesthetic capability of remimazolam was defined as meeting the following dependent variables: • Dependent Variable 1 (DV1): Successful induction of anesthesia without recall • Dependent Variable 2 (DV2): The absence of rescue sedation with other sedatives. • Dependent Variable (DV3): Body movement -Safety endpoint was established by the absence of adverse	Methods used to answer research question: -Efficacy was defined by the absence of clinical signs of awakening which included: • ▲BP • ▲HR • Lacrimation • Perspiration -Awakening was assessed from LoC until the end of the surgery. -Awareness/recall was assessed by using the Brice Questionnaire on Day 1 of the clinical trial, at discharge from the OR, at 24 hours after the end of remimazolam infusion, and the end of the study. -Target infusion rate during the maintenance of anesthesia was defined by the infusion rate, which maintained an optimal anesthetic state for the longest period. The optimal anesthetic state was	Group A: -Efficacy rate = 100% -BIS during maintenance range = 46-68 - Mean ± SD Dose to LoC (mg/kg) = 0.16 ± 0.04 - Mean ± SD Time to LoC (s) = 97.2 ± 23.0 Group B: - Efficacy rate= 100% -BIS during maintenance range= 45-68 - Mean ± SD Dose to LoC (mg/kg) = 0.27 ± 0.08 - Mean ± SD Time to LoC (s) = 81.7 ± 24.9	-The study found 100% efficacy for remimazolam groups a general anesthetic. -LoC was achieved for all patients observed, with the mean time for Group A was 97 seconds (*p* = 0.0139) while Group B was considerably shorter with a mean time of 82 seconds. -Remimazolam induced LoC at mean (5%-95%) with cumulative doses of 0.16 (0.11–0.24) mg/kg in group A and 0.27 (0.17-0.42) mg/kg in group B, respectively. The mean optimal infusion rate (5%-95%) was equal in both treatment arms and comprised: 0.56 (0.13-1.00). No statistically significant	The clinical trial successfully demonstrated the functional anesthetic capability of remimazolam for both groups. 100% of the patients met clinical criteria as evidenced by the absence of intraoperative recall, body movement, and lack of need for rescue medication.	The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. The study's methods and application for remimazolam to be used as a safe and efficacious medication during induction and the maintenance of anesthesia is feasible and highlighted to be 1 of the trial's strengths.

	-The trial was designed as a parallel-group comparative trial recruited at 6 different departments of anesthesiology.	• Met Exclusion Criteria *n* = 1 • Safety Analysis Set (SAF) *n* = 31 • Full Analysis Set (FAS) *n* = 31 • Violations of Protocol *n* = 3 • Per Protocol Set (PPS) *n* = 28 The trial took place in Japan during November 2012 through May 2013.	events (AE) as defined by unintended or an unfavorable sign, which include: • Abnormal laboratory results • Symptoms • Disease following the administration of remimazolam regardless of causation. • Complications or exacerbations of the primary disease diagnosed as surpassing the natural course of the disease	according to the anesthesiologist's judgment. Measurement Scales: Two-sided 95% confidence intervals were calculated for differences between the groups by performing a $\chi 2$ test and a *t*-test.		differences between both groups were found in terms of incidence of AEs, ADRs, BP decreased reported as an AE, or as an ADR over the entire trial period or until completion of intubation.		

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Tang et al.,[10] 2021	- Level 1: Experimental, Randomized control trial (RCT) -The investigators aimed to explore the clinical use of remimazolam benzenesulfonate in surgical cardiac patients undergoing general anesthesia. -The study implemented a random number table to divide 80 patients into 2 anesthesia induction groups. Group 1 patients were induced using remimazolam with a dose of 0.3 mg/kg while Group 2 was induced using 1.5mg/kg of propofol. Hemodynamic parameters, inflammatory stress response indices, respiratory function indices, perioperative indices and adverse reactions in the 2	Inclusion Criteria: -Patients must be between the ages of 19 and 75. -Patients must require heart valve replacement surgery as indicated by the same medical staff in which the study is being conducted. -Patients must be classified as ASA I-III. -Surgical time must be no longer than 7 hours. -Patients must have normal kidney, liver, and circulation function. Exclusion Criteria: -Patients who suffered from hypertension, coagulation dysfunction, viral myocarditis, anemia, myocardial infarction, atrioventricular block, poor blood glucose control or a history of cerebrovascular disease. A total of 80 patients who underwent surgery in the Department of Cardiothoracic	-Independent variable 1 (IV1): Remimazolam at 0.3mg/kg -Independent variable 2 (IV2): Propofol 1.5mg/kg -The following dependent variables were analyzed over time for each group to determine the clinical value of remimazolam for patients undergoing cardiac surgery: • Dependent Variable 1 (DV1): Hemodynamic parameters • Dependent Variable 2 (DV2): Inflammatory stress response indices • Dependent Variable (DV3): Respiratory function indices • Dependent Variable (DV4): Perioperative indices • Dependent Variable (DV5): Adverse reactions	Methods used to answer research question: -Induction of each groups' patients was performed by administering 0.3mg/kg of remimazolam or 1.5mg/kg of propofol within 30 seconds based on their respective groups. Once the bispectral index value (BIS) was less than or equal to 60, 0.2mg/kg of cistacurium and 4 μg/kg of fentanyl was administered. -Throughout the perioperative period, an HP multifunction monitor was used to provide continuous hemodynamic parameters such as heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), and volume per wave index (SVI). • These parameters were then statistically analyzed using the normal distribution test.	Comparison of hemodynamic parameters between the 2 groups (mean ± SD): -Remimazolam (n = 40) • HR (times/minute): ○ T0=76.7 ± 7.1 ○ T1=68.3 ± 6.5 ○ T2=66.8 ± 5.9 ○ T3=78.8 ± 6.6 • MAP (mmHg): ○ T0= 98.4 ± 5.3 ○ T1= 88.3 ± 4.7 ○ T2= 86.7 ± 4.2 ○ T3= 102.1 ± 4.8 • CI (L/minute m^2): ○ T0= 3.67 ± 0.62 ○ T1= 3.52 ± 0.52 ○ T2= 3.58 ± 0.48 ○ T3= 3.57 ± 0.53 • SVI (mL/m2·bpm): ○ T0= 47.83 ± 5.81 ○ T1= 43.80 ± 5.26 ○ T2= 41.94 ± 5.57 ○ T3= 45.80 ± 5.16 -Propofol (n = 40) • HR (times/minute): ○ T0= 78.2 ± 7.7 ○ T1=66.7 ± 6.7 ○ T2=65.1 ± 6.0 ○ T3=80.5 ± 7.3 • MAP (mmHg): ○ T0= 99.6 ± 4.7 ○ T1= 86.0 ± 4.4	-The study did not find a significant difference in hemodynamic parameters during T0. However, there was a significantly higher SVI in the remimazolam group than the propofol group ($p < 0.05$) at T1 and T2. -In regard to the groups' respiratory indices, the study found the oxygenation index value to be higher in the remimazolam group than in the propofol group ($p < 0.05$) during both T1 and T2. -Inflammatory stress response indices IL-6 and TNF-α levels were discovered to be higher 12 hours after	-The study aimed to explore the clinical usefulness of Remimazolam in patients undergoing general anesthesia for cardiac surgery. This study concluded that when compared to propofol, remimazolam benzenesulfonate aided cardiac surgical patients by diminishing hemodynamics fluctuations, incrementing respiratory function and patients' surgical stress response, leading to a reduction in anesthesia-related adverse reactions.	The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. -At the study's date, there were no current studies that investigated the clinical use of remimazolam during general anesthesia in cardiac surgery. The study's strength lies in the ability to conclude the effect and safe use of remimazolam for this patient population and therefore providing more information to create an evidenced based practice clinical anesthesia plan. -A study limitation may have been possible conflict of interest. While the study states that the plan was approved by the Medical Ethics Committee of their respective hospital, and informed consent was obtained by the patients and their

	groups were monitored over time for comparison.	Surgery from August 2020 to April 2021 were included in the study.	-Adverse reactions indices were also investigated for each group during the preanesthetic (T0) induction, after endotracheal intubation (T1), at time of sternal opening (T2), and at the end of bypass use (T3).	• Standard deviation represented by mean ± SD. -Inflammatory stress response was defined by measuring the following levels preoperatively and at 2 or 12 hours. postoperatively: • Serum interleukin-6 (IL-6) levels • Tumor necrosis factor alpha (TNF-α) • Norepinephrine (NE) levels • Epinephrine (E) levels • Cortisol (COR) levels • Blood glucose (GLU) levels -Respiratory function indices were defined by: • Respiratory Index (RI); where RI = P (A-a) O_2/PaO_2 • Oxygenation index (OI); where OI = PaO_2/FiO_2. -Perioperative indices was defined by the following indicators: • Operative time • Intraoperative urine output	○ T2= 83.8 ± 4.5 ○ T3= 103.8 ± 4.2 • CI (L/minute m^2): ○ T0= 3.80 ± 0.60 ○ T1= 3.40 ± 0.48 ○ T2= 3.51 ± 0.50 ○ T3= 3.65 ± 0.49 • SVI (mL/m2·bpm): ○ T0= 49.20 ± 5.63 ○ T1= 40.38 ± 4.95 ○ T2= 38.53 ± 4.86 ○ T3= 43.73 ± 5.57 • t value ○ T0= -1.071 ○ T1= 2.995 ○ T2= 2.918 ○ T3= 1.724 • P value ○ T0= 0.287 ○ T1= 0.004 ○ T2= 0.005 ○ T3= 0.089 Comparison of inflammatory factors between the 2 groups (mean ± SD): -Remimazolam group (*n* = 40) • TNF-α (pg/mL): ○ Before surgery= 1.63 ± 0.46 ○ 12 hours after surgery= 3.74 ± 0.95 • IL-6 (pg/mL): ○ Before surgery= 54.83 ± 12.30 ○ 12 hours after surgery= 87.55 ± 15.40	surgery than preoperatively in both groups. ($p < 0.05$). While the increase in E, NE, and GLU were found to be considerably lower in the Remimazolam group 2 hours after surgery when compared to the Propofol group. ($p < 0.05$). -The study also resulted with notably lower recovery and extubation times in the Remimazolam group than the Propofol group ($p < 0.05$). -Additionally, there were fewer documented adverse reactions in the remimazolam group (10.00%) than in the propofol group (30.00%; $p < 0.05$).		families, it does not state if there was any inconspicuous reason.

				• Operative blood loss • Ascending aorta occlusion time • Coronary bypass (CPB) turnaround time • Recovery time • Extubation time • The use/amount of Fentanyl dosage • Amount of fluid volume administered -The following adverse reactions for both groups were recorded during pre-anesthesia induction phase (T0), after endotracheal intubation (T1), during sternal opening (T2), and once CPB was no longer used (T3): • Nausea • Emesis • Hypotension • Drowsiness • Uroschesis -*t*-tests were performed for comparisons of dependent variables between the groups. -Enumeration data are expressed as percentages, and the $\chi 2$ test was performed for comparison. SPSS version 21.0	• E (pg/μL): ○ Before surgery= 1.58 ± 0.38 ○ 2 hours after surgery= 2.52 ± 0.70 • NE (pg/μL): ○ Before surgery= 2.66 ± 0.48 ○ 2 hours after surgery= 3.38 ± 0.75 • COR (ng/mL): ○ Before surgery= 22.73 ± 4.81 ○ 2 hours after surgery= 34.20 ± 6.85 • GLU (mmol/L): ○ Before surgery= 5.39 ± 0.51 ○ 2 hours after surgery= 6.18 ± 0.62 -Propofol group (n = 40) • TNF-α (pg/mL): ○ Before surgery= 1.80 ± 0.50 ○ 12 hours after surgery= 3.98 ± 1.03 • IL-6 (pg/mL): ○ Before surgery= 50.11 ± 10.86 ○ 12 hours after surgery= 93.28 ± 14.81 • E (pg/μL): ○ Before surgery= 1.49 ± 0.40 ○ 2 h after surgery= 2.86 ± 0.76 • NE (pg/μL):			

				was used for data processing with a test level of $\alpha = 0.05$.	○ Before surgery= 2.48 ± 0.51 ○ 2 hours after surgery= 3.73 ± 0.88 • COR (ng/mL): ○ Before surgery= 21.40 ± 4.36 ○ 2 h after surgery= 31.06 ± 5.72 • GLU (mmol/L): ○ Before surgery= 5.50 ± 0.48 ○ 2 hours after surgery= 6.54 ± 0.75 - t value • TNF-α (pg/mL): ○ Before surgery= -1.583 ○ 12 hours after surgery= -1.083 • IL-6 (pg/mL): ○ Before surgery= 1.819 ○ 12 hours after surgery= -1.696 • E (pg/μL): ○ Before surgery= 1.032 ○ 2 hours after surgery= -2.081 • NE (pg/μL): ○ Before surgery= 1.625 ○ 2 hours after surgery= -1.914 • COR (ng/mL): ○ Before surgery= 1.296 ○ 2 hours after surgery= 2.225 • GLU (mmol/L):			

					○ Before surgery= -0.993 ○ 2 hours after surgery= -2.34 -*p*-value • TNF-α (pg/mL): ○ Before surgery= 0.118 ○ 12 hours after surgery= 0.282 • IL-6 (pg/mL): ○ Before surgery= 0.073 ○ 12 hours after surgery= 0.094 • E (pg/μL): ○ Before surgery= 0.305 ○ 2 hours after surgery= 0.041 • NE (pg/μL): ○ Before surgery= 0.108 ○ 2 hours after surgery= 0.059 • COR (ng/mL): ○ Before surgery= 0.199 ○ 2 hours after surgery= 0.029 • GLU (mmol/L): ○ Before surgery= 0.324 ○ 2 hours after surgery= 0.022 Comparison of oxygenation and respiratory index between the 2 groups (mean ± SD): -Remimazolam (*n* = 40) • OI (mmHg): ○ T1 = 398.6 ± 24.7 ○ T2= 357.6 ± 28.0			

					○ T3= 381.8 ± 30.0 • RI: ○ T1 = 0.59 ± 0.17 ○ T2= 0.90 ± 0.23 ○ T3= 0.50 ± 0.18 • *t* value: ○ T1 = -0.789 ○ T2= -0.812 ○ T3= -1.410 • *p*-value: ○ T1 = 0.432 ○ T2= 0.419 ○ T3= 0.162 -Propofol (*n* = 40) • OI (mmHg): ○ T1 = 390.1 ± 26.3 ○ T2= 338.1 ± 30.5 ○ T3= 359.4 ± 33.8 • RI ○ T1 = 0.62 ± 0.17 ○ T2= 0.94 ± 0.21 ○ T3= 0.56 ± 0.20 Comparison of perioperative indicators between the 2 groups (mean ± SD): -Remimazolam (*n* = 40) • Operative time (minutes)= 249.6 ± 18.5 • Operative blood loss (mL)= 308.4 ± 20.7 • Intraoperative urine volume (mL)= 488.3 ± 81.0			

					• CPB transit time (minutes)= 115.8 ± 9.8 • Ascending aorta occlusion time (minutes)= 76.4 ± 5.1 • Recovery time (minutes)= 121.1 ± 18.0 • Extubation time (minutes)= 158.3 ± 24.7 • Fluid volume (mL)= 1985.6 ± 223.1 • Fentanyl dosage (mg)= 122.8 ± 21.6 -Propofol group (*n* = 40) • Operative time (minutes)= 245.8 ± 17.0 • Operative blood loss (mL)= 304.1 ± 18.6 • Intraoperative urine volume (mL)= 502.7 ± 86.5 • CPB transit time (minutes)= 113.5 ± 10.6 • Ascending aorta occlusion time (minutes)= 78.1 ± 6.3 • Recovery time (minutes)= 140.2 ± 21.5 • Extubation time (minutes)= 174.9 ± 28.6 • Fluid volume (mL)= 2056.7 ± 245.7 • Fentanyl dosage (mg)= 126.4 ± 34.2 - t value			

					• Operative time (minutes)= 0.957 • Operative blood loss (mL)= 0.977 • Intraoperative urine volume (mL)= -0.769 • CPB transit time (minutes)= 1.008 • Ascending aorta occlusion time (minutes)= -1.326 • Recovery time (minutes)= -4.308 • Extubation time (minutes)= -2.778 • Fluid volume (mL)= -1.355 • Fentanyl dosage (mg)= -0.563 - *p*-value • Operative time (minutes)= 0.342 • Operative blood loss (mL)= 0.331 • Intraoperative urine volume (mL)= 0.444 • CPB transit time (minutes)= 0.317 • Ascending aorta occlusion time (minutes)= 0.189 • Recovery time (minutes)= 0.000 • Extubation time (minutes)= 0.007 • Fluid volume (mL)= 0.179 • Fentanyl dosage (mg)= 0.575 Comparison of the adverse reactions between the 2 groups, *n* (%): -Remimazolam (*n* = 40)			

					• Nausea= 1 • Emesis= 0 • Hypotension= 1 • Drowsiness= 1 • Uroschesis= 1 • Incidence of adverse reactions= 4 (10.00) -Propofol group (*n* = 40) • Nausea = 3 • Emesis = 1 • Hypotension = 3 • Drowsiness = 3 • Uroschesis = 2 • Incidence of adverse reactions = 12 (30.00) - $\chi 2$ value: 5.000 - *p*-value: 0.025			

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Singh et al.,[8] 2010	-Level 1: Experimental, Randomized control trial (RCT) -Each patient was randomized into 1 of the 4 induction agent groups by the sealed envelope technique. -The study aimed to establish a comparison between the hemodynamic impact of propofol, etomidate, thiopentone, and midazolam during anesthesia induction in patients with left ventricular dysfunction (LVD) and coronary artery disease (CAD). -Sixty patients suffering from CAD and LVD who were scheduled for elective coronary artery bypass (CABG) surgery were recruited for the study. The patients were randomly assigned to 1 of the 4 corresponding induction agents. The intravenous induction agent was administered for	Inclusion criteria: -Patients with CAD and LVD scheduled for elective CABG -Ejection Fraction (EF)<45% Exclusion criteria: -Patients with the following associated conditions: • Valvular heart disease • Congestive cardiac failure • Persistent arrhythmias • Mechanically ventilated patients • Intra-aortic balloon pump patients • Emergent surgical patients • Adrenal insufficiency • Steroidal use in the 6 months prior to surgery • Patients with severe systemic non-cardiac disease, other than hypertension and diabetes. This clinical trial was conducted at the All-Indian Institute of Medical Sciences, New Delhi, India.	-Independent variable 1 (IV1): Etomidate 0.2mg/kg (Group E) -Independent variable 2 (IV2): Midazolam 0.15mg/kg (Group M) -Independent variable 3 (IV3): Thiopentone 5mg/kg (Group M) -Independent variable 4 (IV4): Propofol 1.5mg/kg (Group P) -Dependent variable 1 (DV1): Heart rate (beat/minute) -Dependent variable 2 (DV2): MAP (mmHg) -Dependent variable 3 (DV3): Stroke volume index ($ml/b/m^2$) -Dependent variable 4 (DV4): Cardiac Index ($l/minute/m^2$) -Significant hemodynamic changes was defined by an increase in heart	Methods used to answer research question: -All patients continued their cardiac medication, except for angiotensin converting enzyme (ACE) inhibitors, up to the morning of the surgery. -All patients received 10mg of oral diazepam the night before surgery. -0.2mg/kg of intramuscular morphine with 25mg promethazine 1 hour prior to anesthesia induction. -Standard monitoring was initiated once patient was in the operating room and local anesthesia was implemented to place a right radial arterial line and a right internal jugular vein central venous line. -The Flo Trac TM connected to the radial arterial cannula to retrieve hemodynamic parameters such as: • Cardiac output (CO) • Cardiac index (CI) • Stroke volume (SV) • Stroke volume index (SVI) • Stroke volume variation (SVV) • Systemic vascular resistance index (SVRI) -Over 1 minute, all patients received 4mcg/kg of IV fentanyl. After 5 minutes, baseline data was obtained. The induction of general anesthesia using the groups' specified agent was then initiated and administered over a period of 60-90 seconds.	Maximum percentage change from baseline in hemodynamic parameters after induction and after intubation: -Induction: • Group E: ○ HR = -8% ○ SVI = -34% ○ CI= -38% ○ MAP= -27% ○ SVRI= +9% • Group M: ○ HR = -15% ○ SVI = -27% ○ CI= -36% ○ MAP= -31% ○ SVRI= -4% • Group T: ○ HR = -7% ○ SVI = -31% ○ CI= -38% ○ MAP= -29% ○ SVRI= +8% • Group P: ○ HR = -10% ○ SVI = -29% ○ CI= -38% ○ MAP= -32% ○ SVRI= -9%	-Once comparisons were made, the study found all baseline hemodynamic variables were comparable between the groups. -There was found to be a marked decrease from baseline of p = 0.001 in each group in HR, MAP, CI, and SVI after induction. Group T demonstrated the least decrease in HR from baseline (-7%) while Group M led to the maximum decrease in HR of -15%. Group M had the least decrease in SVI (-27%) and Group E showed the maximum decrease of -34%. CI varied from -36 (Group M) to -38 (Groups E, T, and P). After induction, 1 patient in Group P needed active volume resuscitation when the CI decreased	The study concluded that each of the 4 anesthetic agents were acceptable for induction in patients with CAD and LVD despite a 30% to 40% decrease in the cardiac index. The study speculates the moderate decrease in CO during anesthesia induction may have been caused by a decline in arterial pressure and SV. All 4 groups had a comparable decrease in hemodynamics during induction, which may be attributed to the loss of sympathetic stimulation during this time rather than the anesthetic drug itself as each	The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. Limitations of the study: -The decrease ranging from 30% to 40% observed in blood pressure and CI can be harmful in patients who have limited cardiac reserves. The authors believe a slower induction dose given over 2-4 minutes instead of 60-90 seconds may cause a less hemodynamic decline. -Additionally, as the study

	over 60-90 seconds. Baseline hemodynamic data was recorded prior to induction and then at 1-minute intervals from induction until 7 minutes after intubation. Hemodynamic data recorded was then compared between the groups.		rate of 20 beats/minute or 20mmHg in blood pressure. -End of induction was defined by the loss of eyelash reflex and lack of response to verbal commands. -Endpoint of the study was defined as 7 minutes after intubation.	-Hemodynamic data was collected at 1-minute intervals from induction until 7 minutes after intubation. -0.1mg/kg of Vecuronium bromide was given 3 minutes after the end of induction to assist in tracheal intubation. -Data was analyzed using the SPSS version 15 software with patients' characteristics and hemodynamic variables expressed as a mean of standard deviation. -A 2-way ANOVA test was implemented to analyze the pair wise hemodynamic data of each group at their minute intervals followed by a post-hoc analysis using Fisher's Least Significant Difference (LSD) time trend method. This was then followed by a post-hoc analysis using the Bonferroni method. -The relationship between CVP and LVD was analyzed using the Pearson's correlation coefficient. -For each of the comparisons performed during the study a *p*-value of < 0.05 was deemed as significant. -A power analysis from previous studies concluded that a sample size of 15 patients per group was needed to accomplish a power of 80% and a α 0.05 for detection of the desired hemodynamic changes.		below 1.8 L/minute/m^2. The decrease in MAP ranged from -27 (Group E) to -32% (Group P). The MAP changes were similar across the 4 groups ($p = 0.69$) followed by subsequent variable changes in SVRI. -These same hemodynamic variables increased above baseline a minute after intubation for all 4 groups, which revealed no changes when an intergroup comparison was performed during this period. -Midazolam was found to be the most successful in preventing the stress patients experience during intubation. During this period, Midazolam displayed an increase in HR of 4% ($p = 0.12$) from baseline and a decrease in MAP from base of only -1% ($p = 0.77$). These values were not found to be statistically	agent does not provide benefit without a disadvantage. While Midazolam had the highest depressive effect it may be beneficial to certain patients for its blunting effect to the intubation stress response. The researchers believed that the hemodynamic effects on cardiac patients receiving anesthetic induction agents hinge greatly on the technique, skill, and experience of the administrating anesthesia provider. They further hypothesized that speed of induction and dose adjustments are more likely of greater importance than the	was designed to represent clinical practice, the concomitant opioid dose of Fentanyl may have affected patient hemo-dynamics. However, a small dose such as 4 μ/kg has been shown to produce minimal cardio-vascular impact. -A strength of the study was how the authors sought out to investigate the effects of each the induction agent for its ability in clinical use rather than to study each drug as the sole anesthetic.

						significant. On the contrary, Etomidate was the least valuable for intubation stress response with a statistically significant increase from baseline in both heart rate (p = 0.001) and mean arterial pressure (p = 0.001), 1 minute after intubation. Intragroup comparison revealed that there was no significant change in CVP and SVV during induction and intubation, while the effects on SVRI were variable (p = 0.05 for each). Baseline CVP value ranged from 3 to 15 mmHg with wide variation and did not correlate with the degree of ventricular dysfunction (r = +0.10, p = 0.46).	individual drug that is used.	

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Hannam et al.,[24] 2019	-Level I: Experimental, Randomized Control Trial with both unblinded and blinded phases -The study aimed to compare the hemodynamic effects of etomidate and propofol as induction agents in cardiac surgical patients. -Patients were randomly chosen to be induced by using either etomidate or propofol. During the first phase (Phase I) of the study, patients were randomly selected to be induced with either anesthetic agent; however, the selected agent was unblinded, also known as open label. During Phase II, both clinical and the study's staff were blinded to the induction agent of choice. After induction, mean arterial blood pressure (MAP) and the use of vasopressive boluses	Inclusion Criteria: -Adults 18 years or older. -ASA of II-IV -Undergoing elective cardiac surgery: • Coronary artery bypass (CABG) • Valve surgery • Combination of CABG and valve surgery • Thoracic aorta surgery Exclusion Criteria: -Allergy to either of the induction agents -Patients who were scheduled for transplant surgery Flow of participants through the study: -Scheduled for inclusive cardiac surgery (n = 937) -Screened for eligibility based on the availability of a researcher (n = 338) -Screened and excluded (n = 154) -Informed consent provided and patient enrolled (n =184) -Withdrawn (n = 28) Randomized (n =156) -Allocated to etomidate (n = 78) • Excluded: ○ Anesthetist declined to participate (n = 1)	-Independent variable 1 (IV1): Etomidate -Independent variable 2 (IV2): Propofol -Independent variable 3 (IV3): blinded -Independent variable 4 (IV4): Unblinded -Dependent variable 1 (DV1): MAP-time integral (AUC) -Dependent variable 2 (DV2): Use of vasopressors -Baseline MAP was defined as the mean MAP over the 3-minute period prior to induction. -AUC was defined as the area under the baseline MAP within the 10 minutes after induction. -Clinically important	Methods used to answer research question: -Patients were randomly picked to receive either propofol or etomidate during surgical induction. In Phase I of the study, the anesthesia provider was provided a randomization code and was not blinded to the induction agent that would be used. In Phase II of the study both the clinical staff and those conducting the study were blinded to the induction agent. This was accomplished by using a white emulsion solution of etomidate, which is visually identical to propofol. -Induction of anesthesia was accomplish by titrating the assigned anesthetic to achieve loss of responsiveness to verbal commands. -The anesthetist determined the appropriate blood pressure level for the patient and administered either a bolus dose of metaraminol (0.25mg-0.5mg) or ephedrine (3-6mg) for blood pressure support when needed. The patient was intubated by administering a neuromuscular blocking agent, volatile anesthetics were used to maintain anesthetic depth prior to cardiopulmonary bypass.	AUC (mmHg/s): findings Mean (standard deviation, SD) after correction for phase, baseline MAP and anesthesiologist. -Etomidate: • Phase I (n = 36) = -6011 (5567) • Phase II (n = 39) = -7179 (5356) • Total = -6595 (5404) -Propofol: • Phase I (n = 40) = -7956 (5410) • Phase II (n = 35) = -9722 (5346) • Total = -8839 (5355) -All data: • Phase I = -6983(5738) • Phase II = -8450 (5481) • Total = -7942 (7858) Vasopressor administrations: -Etomidate: • Phase I (n = 36) = 3 • Phase II (n = 39) = 14 • Total= 17 • Total needing any vasopressor= 10 -Propofol: • Phase I (n = 40) = 15 • Phase II (n = 35) = 18 • Total = 33 • Total needing any vasopressor = 21	Primary Endpoint: -The findings demonstrate the AUC (SD) for both blinded and unblinded for etomidate as -6595 (5404) mmHg s and -8839(5355) mmHg s for propofol. The results lead to a mean difference of 2244 (95% CI, 581-3906) mmHg s. This amount signifies a 34% (95% CI, 9-59%) greater reduction with the use of propofol, which is higher than the predefined level of clinical importance. Secondary Endpoint: -The study recorded a total of 21 patients out of the 75 in the propofol group were administered vasopressors during the first 10 minutes after	The study results concluded that etomidate had a superior hemodynamic effect compared to propofol which caused a 34% greater reduction in AUC. This result was deemed clinically significant despite the more frequent use of vasopressors within the propofol group. In fact, the authors hypothesized that the increased use of vasopressors in the propofol group may have reduced the magnitude of its mean AUC of 34%.	-The RCT is rated a Level I-High Quality of Evidence based on the John Hopkins Level of Evidence Table. This study is the only study up to its date that compared the effect of both medications using a blinded and open label methods. However, while blinding the anesthesia provider was found to be statistically non-significant, it possibly led to a change in clinical practice. The authors found a 3.2-fold increase per kg dose of etomidate in the blinded phase than unblinded.

	were documented for each group.	○ Participant withdrew from the study (*n* = 1) ○ Blood pressure trace in electronic record corrupted/unusable ○ Analyzed (*n* = 75) -Allocated to propofol (*n* = 78) • Excluded: ○ Procedure did not go ahead (*n* = 2) ○ Electronic record unavailable on hospital server (*n* = 1) ○ Analyzed (*n* = 75) The study was conducted at the Green Lane Cardio-thoracic Surgery Unit in Auckland, New Zealand during August 2014-2015.	difference in MAP was stated as 33%. -The primary endpoint for this study was to analyze the effect on the patients' baseline MAP during a 10-minute interval after induction. Secondary endpoints sought by the study was to document the need use of vasopressor during the use of the anesthetic agent and the effect of blinding on the endpoints.	-Direct measurements of blood pressure was obtained by the insertion of an arterial catheter that was placed prior to the induction of anesthesia. Central venous catheter was placed after induction. -AIMS was used to automatically record MAP at 30-second intervals. An observer documented the amount of vasopressor used during the first 10 minutes after induction. -The primary endpoint comparison for each agent was achieved using a general linear model (GLM). -The use of vasopressor drugs was assigned a numeric number (no bolus = 0, 1 or more boluses s= 1) to then perform a logistic regression in which the results concluded as odds ratios (OR) with 95% confidence interval (CI). -Primary endpoints for both phases were compared between groups with stratification factors controlling for covariates of anesthetist, study phase, and baseline MAP. -Secondary endpoint was compared within a test model.		induction. The etomidate group administered to a total of 10 patients out of 75. These results give a OR of 1.84 (95% CI, 0.47-7.27: P.0.38) in Phase I (open label). -Regression analysis concluded that phase (P=0.31) nor induction agent (P=0.38) were suggestive predictors of vasopressor administration. -Analysis between the effect of blinding or unblinding was concluded to be non-significant with $p = 0.73$ and 0.90, respectively.		This was thought to be attributed to the milky color of etomidate during this phase, which led the anesthesia provider to believe it was in fact propofol.

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Hailu et al.,[25] 2021	-Level I: Experimental, Randomized control trial with both unblinded and blinded phases -In this double-blind randomized control trial, the authors aimed to explore the usefulness of ketofol as an induction medication versus propofol. -Patients were randomly placed into 1 of 2 groups where they would receive either propofol or ketofol as an induction medication for general anesthesia. The change in systolic blood pressure (SBP), heart rate (HR), and mean arterial pressure (MAP) during 30 minutes after induction were recorded and analyzed.	Inclusion Criteria: -Adult 18-65 years of age -ASA II-III -Undergoing elective surgery under general anesthesia Exclusion Criteria: -Obstetric patients -Neurosurgical patients -Patients undergoing ear, nose, or throat (ENT) surgery -Patients on long term use of opioids, adjunctive medications, or on psychotropic drugs -Any allergy or contraindication to ketamine or propofol -patients who were in pain or treated for long term pain Flow of participants through the study: -Assessed for eligibility (n = 62) -Randomization (n = 62) -Allocated to ketofol group and received allocated intervention (n = 31) -Allocated to propofol group and received allocated intervention (n = 31) -Lost to follow up (n = 0) -Excluded from analysis (n = 0)	-Independent variable 1 (IV1): Propofol -Independent variable 2 (IV2): Ketofol -Dependent variable 1 (DV1): SBP -Dependent variable 2 (DV2): MAP -Dependent variable 3 (DV3): HR -Dependent variable 4 (DV4): Adverse reactions -Primary endpoints were defined by analyzing SBP, MAP, and HR at baseline, immediately after induction and at 5-minute intervals during the first 30 minutes after induction. -Baseline hemodynamics was defined as the average of the primary endpoints at 1-minute, 3-minute, and 5-minute points before induction.	Methods used to answer research question: -Patients who met inclusion criteria were randomly allocated an induction medication group of either ketofol or propofol by drawing 1 of the 2 labels in a sealed envelope which contained labels of either '01'(ketofol) or '02' (propofol). -The study was considered double blinded as both the participant and the anesthesia provider were blinded to the allocated induction medication. -Propofol induction was achieved using weight-based dosing at 2mg/kg. The indicated amount was then mixed with normal saline to give a total volume of 20ml. Ketofol induction was calculated by weight-based dosing of 0.75mg/kg of ketamine and 10.5mg/kg of propofol were mixed with normal saline for a final volume of 20ml. The total of 20ml in each syringe would assure the blinding to treatment assignment to data collectors or anesthesia providers. -The amount of vasoactive, analgesic, and antiemetic medications was recorded	Hemodynamic Variables (Mean ± SD): -Ketofol (n = 31) • Baseline: ○ SBP 125.03 ± 12.81 ○ MAP 91.94 ± 8.40 ○ HR 82.87 ± 12.19 • Immediately after induction: ○ SBP 126.32 ± 16.51 ○ MAP 90.87 ± 12.12 ○ HR 88.87 ± 11.45 • @5th minutes ○ SBP 122.97 ± 15.17 ○ MAP 90.74 ± 11.15 ○ HR 89.00 ± 10.96 • @10th minutes ○ SBP 121.90 ± 14.86 ○ MAP 90.00 ± 12.00 ○ HR 83.42 ± 11.07 • @15th minutes ○ SBP 120.06 ± 14.32 ○ MAP 89.26 ± 11.13 ○ HR 82.39 ± 12.27 • @20th minutes ○ SBP 121.29 ± 8.87 ○ MAP 88.42 ± 7.87 ○ HR 83.55 ± 11.83 • @25th minutes ○ SBP 119.77 ± 11.83 ○ MAP 89.13 ± 8.83 ○ HR 80.42 ± 11.80 • @30th minutes	Primary endpoint: Both the mean systolic blood pressure and mean arterial pressure were significantly decreased in the propofol group immediately after induction, at 5th minute, 10th minute, and 15th minute compared to the baseline value with a statistically significant value of $p < 0.05$. There was a significant increase in mean heart rate in the ketofol group immediately after induction and on the 5th minute after induction compared to the baseline value (p=0.001 and p=0.022 respectively). Secondary endpoint:	The authors concluded that the administration of ketofol for the induction of general anesthesia had better hemodynamic stability when compared to propofol during the first 30 minutes after induction, while there was no statistical significance in the difference between the groups in terms of pain or PONV.	-The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. Strengths of the study include the fact that it was conducted as a double-blind RCT and included a homogeneous population regarding socio-demographic aspects in both groups. The study's limitations included lack of control over the confounding factors such as incision size and shorter duration of postoperative follow-up.

		The study was conducted from 08/20/2020 to 12/30/2020.	-Adverse reactions/Secondary endpoints were defined as: • Postoperative pain • Nausea • Vomiting	during the analyzed period. Operative skin incision was not initiated until 15 minutes after induction when the depth of anesthesia was maintained. This assured that pain would not influence the primary endpoints. -Suxamethonium 1-2 mg/kg was used for intubation while vecuronium 0.07-0.1 mg/kg was used for maintaining relaxation after which patients were mechanically ventilated. Anesthesia was maintained with isoflurane 1.2%. -After the normal distribution of data was tested analytic statistics were calculated for variables in the study using mixed ANOVA, independent samples *t*-test, and Mann Whitney U-test as appropriate, and for categorical data Chi-square test or fisher's exact test was used for analysis. *P*-value < 0.05 is considered statistically significant with a power of 90%	○ SBP 123.68 ± 13.94 ○ MAP 89.00 ± 9.27 ○ HR 81.23 ± 8.81 -Propofol (*n* = 31) • Baseline: ○ SBP 128.35 ± 10.40 ○ MAP 94.19 ± 7.95 ○ HR 86.9 ± 9.91 • Immediately after induction: ○ SBP 117.74 ± 19.65 ○ MAP 87.42 ± 12.96 ○ HR 86.97 ± 13.73 • @5th minutes ○ SBP 110.32 ± 15.59 ○ MAP 81.77 ± 13.22 ○ HR 87.29 ± 13.40 • @10th minutes ○ SBP 112.35 ± 15.46 ○ MAP 83.84 ± 12.52 ○ HR 83.94 ± 11.35 • @15th minutes ○ SBP 116.61 ± 19.27 ○ MAP 85.71 ± 15.34 ○ HR 86.90 ± 12.35 • @20th minutes ○ SBP 119.87 ± 18.70 ○ MAP 88.58 ± 12.65 ○ HR 88.10 ± 10.45 • @25th minutes ○ SBP 121.13 ± 16.73 ○ MAP 89.45 ± 12.63 ○ HR 86.68 ± 12.30 • @30th minutes ○ SBP 123.07 ± 17.43 ○ MAP 90.13 ± 10.13 ○ HR 84.23 ± 10.10	-The results demonstrated that none of the patients in either group reported pain as assessed by the VNRS score. Additionally, it was found that the ketofol group had 9.7% (3 patients) who developed PONV while the propofol group had 6.5% (2 patients). However, after a Fisher's exact test was conducted, *p*-value= 1.000 defining no statistically significant association between the 2 studies in reference to PONV.		The authors recommend to future researchers to use a larger sample size with the use of invasive BP measurement in a multicenter RCT.

					Secondary endpoints: -PONV (Yes/No): • Ketofol= 3/28 • Propofol= 2/29 -PO Pain (Yes/No): • Ketofol= 0/31 • Propofol= 0/31 -*p*-value = 1.000			

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Claeys et al.,[26] 1988	-Level II: Quasi-experimental study -The study sought to investigate hemodynamic effects of propofol when used for both induction and maintenance of anesthesia. The results were then compared to those acquired in similar studies using other IV anesthetics.	Inclusion Criteria: -Adult 50-75 years of age -ASA II-III -Undergoing total hip replacement surgery under general anesthesia Exclusion Criteria: -Cardiac dysfunction -Hepatic dysfunction -Propofol induction group (n = 10)	-Independent variable 1 (IV1): Propofol -Independent variable 2 (IV2): Althesin -Independent variable 3 (IV3): Methohexitone -Independent variable 4 (IV4): Thiopentone -Dependent variable 1 (DV1): Systolic arterial pressure (SAP) -Dependent variable 2 (DV2): Diastolic arterial pressure (DAP) -Dependent variable 3 (DV3): HR -Dependent variable 4 (DV4): Cardiac output (CO) -Dependent variable 5 (DV5): Stroke volume (SV) -Dependent variable 6 (DV6): Systemic vascular resistance (SVR)	Methods used to answer research question: -All patients were placed an arterial radial transducer line in their non-dominant arm, in addition to a balloon-tipped thermodilution pulmonary artery (PA) catheter via the right internal jugular, for continuous hemodynamic monitoring. -Manipulation of the patient was terminated 20 minutes before obtaining baseline values and surgical stimulation was postponed during the 60-minute evaluation period after induction. -After baseline values were recorded, induction was initiated by inducing patients using 2mg/kg over 30 seconds while concurrently starting a zero-order infusion of propofol at a rate of 6mg/kg/hour lasting 60 minutes to maintain unconsciousness. -Hemodynamic measurements were obtained at baseline, 2, 6, 10, 15, 20, 30, 45, and 60 minutes after the initial propofol administration. -Statistical analysis of the hemodynamic measurements were determined using the	*Statistically significant variations induced by propofol expressed as percent difference from baseline value: -Propofol Induction 2mg/kg (n = 10): • HR= + 10% • SAP= -28%* • DAP= -19%* • CO= - 7% • SV= -17% • SVR= -21%* • CVP= -20% • AWP= -14% • RPP= -22%* -Propofol Maintenance 6mg/kg/hr (n = 10) • HR= -2% • SAP= -30%* • DAP= -25%* • CO= - 2% • SV= -1% • SVR= -30%* • CVP= -13% • AWP= -12% • RPP= -31%*	Primary endpoint: -Statistical analysis found the mean values of PAP, HR, CO, CVP, and PCWP change was statistically inconsequential during all the collected times. However, SAP and DAP declined rapidly and significantly by 28% and 19% respectively immediately after the administration of the induction dose of propofol. During the maintenance stage, SAP and DAP continued to decrease to 30% and 25% respectively (p < 0.001). Changes in blood pressure mirrored the decrease in SVR on induction (-22%) and maintenance (-31%) (p < 0.001). while RPP remained decreased during the entire trial. SV decreased minimally 2 minutes after induction and gradually returned to baseline values thereafter.	Upon comparison, the authors results confirmed the hemodynamic effects of propofol during induction are comparable to those found for other anesthetics. Apart from the initial tachycardia seen with thiopentone and methohexitone, propofol produced similar hemodynamic changes following the induction of anesthesia. Regarding the maintenance of anesthesia with a propofol infusion, the authors concluded that the resulted hemodynamic values were similar to those obtained in the comparable studies where they used Althesin,	-The RCT is rated a Level II-Low Quality of Evidence based on the John Hopkins Level of Evidence Table. Limitations: -The study lacked a sufficient sample size for its study design. -The study did not state how the 10 patients were chosen for the study. -The study did not state if there were any limitations or conflict of interest. -The authors did not study the comparative induction agents themselves.

			-Dependent variable 7 (DV7): Central venous pressure (CVP) -Dependent variable 8 (DV8): Arterial wedge pressure (AWP) -Dependent variable 9 (DV9): Rate pressure product (RPP)	Student's *t*-test with Bonferroni correction.			minaxolone, methohexitone, and thiopentone as maintenance agents. The authors believed the arterial hypotension associated with the induction and infusion of propofol was caused secondary to a decrease in SVR without the compensatory increases in heart rate or cardiac output.	

*Statistically significant results.

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Chen et al.,[27] 2020	-Level 1: Experimental, Randomized control trial (RCT) -The study was a multicentered, blinded, active-controlled, non-inferior phase III trial.	Inclusion Criteria: -Scheduled for therapeutic or diagnostic colonoscopy -18-65 years old -ASA I-II -BMI = 18-30kg/m^2 Exclusion Criteria: -Patient was about to receive endotracheal intubation or laryngeal mask -Needed a complicated endoscopic procedure -Patient has suffered from acute heart failure, unstable angina, and myocardial infarction within 6 months of procedure -Resting heart rate less than 50 beats/minute -Grade III atrioventricular block -Severe arrhythmia -Moderate to severe heart valve disease -Patients with severe respiratory disease -Patients with psychiatric disorders -Grade IV mallampati -Anemia or thrombocytopenia	-Independent variable 1 (IV1): Remimazolam bolus 5mg -Independent variable 2 (IV2): Propofol bolus of 1.5mg/kg -Dependent variable 1 (DV1): Procedure success -Dependent variable 2 (DV2): Hypotension -Dependent variable 3 (DV3): Hypotension requiring treatment -Primary endpoints was the successful completion of the procedure by meeting the following conditions: • Completion of the procedure • No need for rescue sedative medication • No requirement for more than the maximum 5 top-offs within any 15-minute period	Methods used to answer the question: -Induction of sedation was achieved by administering either 5.0mg or 1.5mg/kg of propofol intravenously. -The procedure was started when adequate sedation, defined by a Modified Observer's Assessment of Alertness/Sedation score (MOAA/S) score of ≤3 was achieved -If sedation were insufficient after the initial dose, the patient would receive an additional dose of remimazolam 2.5mg/time or propofol 0.5mg/kg/time, respectively. -Extra quantities were limited to a maximum of 5 doses in a 15-minute window -Noninferiority test was performed on primary endpoints between the 2 groups	Remimazolam (*n* = 194) -Procedure success, No (%) = 188 (96.91) • 95% CI= (94.47, 99,34) -Difference in rate=-3.09% • -95% CI = (-5.53%, -0.66%) -Noninferiority margin= 8.00% -Hypotension, No. (%) = 46 (23.71) -Hypotension requiring treatment, No (%) = 7 (3.61) Propofol (*n* =190) -Procedure success, No (%) = 190 (100) • 95% CI= (100, 100) -Difference in rate=-3.09% • -95% CI = NA -Noninferiority margin= NA -Hypotension, No. (%) = 97 (51.05) -Hypotension requiring treatment, No (%) = 14 (7.37)	The study resulted in a sedation success rate of 96.91% in the remimazolam group and 100% in the propofol group, with a difference in the rate of -3.09% confidence interval (CI) of -5.53% to approximately -0.66%. The efficacy of remimazolam was categorized as non-inferior to propofol as the lower limit of 95% CI was more significant than the non-inferiority margin of -8%. Furthermore, the remimazolam group demonstrated significantly fewer rates of hypotension (23.71%) when compared to propofol (51.05%) ($p < 0.001$)	The trial concluded that the sedation efficacy of the fast-acting benzodiazepine sedative agent, remimazolam tosylate, was non-inferior to propofol. Additionally, remimazolam proved much safer than propofol for patients undergoing colonoscopy.	-The RCT is rated a Level I-Good Quality of Evidence based on the John Hopkins Level of Evidence Table. -Authors stated they had no conflict of interest. Limitations: -Most of the enrolled patients were middle aged with fewer elderly patients. -All the hospital setting in which the trial took place were considered top rated. Therefore, results may differ in a lower-level hospital secondary to technique differences.

		Flow of participants through the study: Assessed for eligibility (*n* = 458) -Met exclusion criteria (*n* = 52) -Withdrew informed consents (*n* = 18) -Patients recruited (*n* = 388) • Remimazolam group (*n* = 196) ○ Excluded due to cardiac issues (*n* = 2) ○ Received intervention (*n* = 194) • Propofol group (*n* = 192) ○ Excluded for fever (*n* = 1) ○ Excluded for hypertension (*n* = 1) ○ Received intervention (*n* = 190)	-Secondary endpoints were defined as: • Induction time • Hypotension • Hypotension requiring treatment -Hypotension was defined as the reduction of SBP of greater or equal to 20% when compared to baseline or an SBP ≤80 mmHg at any time during the procedure.	with a margin set at 8% with one-sed type I error rate of 0.025. -Noninferiority was determined if the lower limit of the 95% confidence interval (CI) of the difference of procedure success rate was more than -8%. -P value <0.05 was considered statistically significant. -SAS 9.4 was used for statistical analysis -The Chi-square test, Fisher's exact test or Wilcoxon rank-sum test were used for comparison of the 2 groups. -Continuous data was described as a mean and standard deviation (SD). -Comparisons of continuous data between the 2 groups were formulated by Student's *t*-test.				

Results

General Anesthesia

Hailu et al.[25] conducted a double-blind RCT to explore the usefulness of ketofol as an induction medication versus propofol.[25] Patients were chosen from 18-65 years of age who were designated an ASA II-III and were undergoing elective surgery under general anesthesia. Patients were randomly placed into 1 of 2 groups where they would receive either propofol (n = 31) or ketofol (n = 31) as an induction medication. Propofol induction was achieved using weight-based dosing at 2mg/kg. [25] The indicated amount was then mixed with normal saline to give a total volume of 20 ml. Ketofol induction was calculated by weight-based dosing of 0.75mg/kg of ketamine, and 10.5mg/kg of propofol was mixed with normal saline for a final volume of 20 ml. The total of 20ml in each syringe would ensure the blinding to treatment assignment to data collectors or anesthesia providers. Primary endpoints were defined by analyzing systolic blood pressure (SBP), MAP, and HR at baseline, immediately after induction, and at 5min intervals during the first 30 minutes after induction.[25]

The findings demonstrated both the mean SBP and MAP were significantly decreased in the propofol group immediately after induction (SBP = 117.74 ± 19.65; MAP = 87.42 ± 12.96), at the 5th minute (SBP =110.32 ± 15.59; MAP = 81.77 ± 13.22), 10th minute (SBP = 112.35 ± 15.46; MAP= 83.84 ± 12.52), and 15th minute (SBP = 116.61 ± 19.27; MAP = 85.71 ± 15.34) compared to the baseline value with a statistically significant value of ($p < 0.05$).[25] There was a substantial increase in mean heart rate in the ketofol group immediately after induction (HR=88.87 ± 11.45) and on the 5th minute (HR= 89.00 ± 10.96) after induction compared to the baseline value (p= .0.001 and p= 0.022 respectively). The authors concluded that the

administration of ketofol for the induction of general anesthesia had better hemodynamic stability when compared to propofol during the first 30 minutes after induction.[25]

Chae et al.[20] performed a Level I double-blinded, single-center, 6-arm experimental RCT.[20] The authors randomly allocated 120 patients undergoing general anesthesia into 6 groups of bolus intravenous (IV) remimazolam for induction of anesthesia. Their goal was to investigate the bolus dose needed for loss of consciousness (LoC) while evaluating hemodynamic variables, and other factors, during this time.[20] Patients included adults over 18 years of age, designated an ASA I-III, and undergoing elective surgery under general anesthesia. Each of the 6 groups would be induced using remimazolam at different dosages; Group 1= 0.02mg/kg (*n* = 20), Group 2= 0.07mg/kg (*n* = 20), Group 3= 0.12mg/kg (*n* = 20), Group 4= 0.17mg/kg (*n* = 20), Group 5= 0.0.22mg/kg (*n* = 20), Group 6= 0.27mg/kg (*n* = 20).[20] Patients were administered their group-designated dose, and hemodynamic variables were evaluated every 30 seconds for the first 5 minutes during anesthesia induction. LoC was evaluated every 10 seconds from the point of induction agent administration. The primary endpoints were defined as the remimazolam dosage needed to safely reach LoC of 50% (ED50) and 95% (ED95) of the general population. The dose-response relationships for LoC and MAP would then be evaluated.[20]

The findings revealed that a 0.11mg/kg dose would be needed to safely induce 50% of the general population (ED50), while a dose of 0.19mg/kg was necessary for an ED95.[20] Additionally, a maximum decrease in MAP of 27.8% was seen with an ED 50 of 0.14mg/kg, which is greater than the recommended dose they found needed (0.11mg/kg) to induce 50% of the population safely. Similarly, the maximum decrease in MAP for ED95 was found at a dose of 2.60mg/kg, much larger than the recommended ED95 dose of 0.19mg/kg. Therefore, the study

concluded that remimazolam could be safely employed without producing substantial hemodynamic instability.[20]

Doi et al.[21] conducted a Level I multicenter, single-blind, parallel-group, experimental RCT to compare the efficacy and safety of remimazolam versus propofol for general anesthesia.[21] Patients were randomly chosen to receive either remimazolam or propofol to allocate to 1 of 2 medication groups. The remimazolam group was divided into 2 groups with different induction doses using a double-blinded technique.[21] Patients older than 20, with an ASA of I-II, weighed less than 100kg and underwent elective surgery requiring general anesthesia with tracheal intubation. Surgery would require a hospitalization stay of 3 days or greater.[21] Group 1 (n = 138) and 2 (n = 134) were induced via a continuous infusion of 6 or 12mg/kg/h (respectively) for up to 2.5min. Group 3 (n = 70) was induced with a 2.0-2.5mg/kg bolus of propofol infused over 1 minute. Both groups would receive an induction dose until LoC with safety endpoints established by the absence of adverse events (AE), such as a decrease in MAP.[21] The investigative medication was discontinued, and a rescue sedative was administered if LoC was not achieved within 2.5min. Efficacy was defined by the lack of clinical signs of awakening, which included ▲BP and ▲HR, successful induction of anesthesia without recall, the absence of rescue medication with other sedatives, and lack of body movement.[21]

The results exposed 100% efficacy rates in all 3 treatment groups, with the non-inferiority of remimazolam compared to propofol confirmed with a 95% (CI− 0.0487; 0.0250), which is higher than the noninferiority threshold.[21] However, both remimazolam groups demonstrated a longer time to LoC (mean: 102.0 s vs 88.7 s vs 78.7 s, respectively). The incidence of adverse reactions (ADRs) was higher in the propofol group (61.3%) compared to both remimazolam groups (Group 1 = 39.3%; Group 2 = 42.7%).[21] Similarly, the propofol group

experienced a decrease in blood pressure in 49.3% of patients, compared with the remimazolam groups, whose patients experienced hypotension of 20% in Group 1 and 24% in Group 2. The authors concluded that the efficacy of remimazolam as a sedative-hypnotic for the induction of general anesthesia is non-inferior to propofol.[21]

Dai et al.[22] executed a Level I experimental RCT intending to evaluate the safety and efficacy of remimazolam compared to propofol during the induction of general anesthesia.[22] Patients scheduled for elective surgery were randomly placed in 1 of 4 groups. The trial included patients between the ages of 18 and 65 with an ASA rating of I-II and a BMI between 18kg/m2 and 30kg/m2.[22] During induction, all patients received a single dose of remimazolam (R1 group [n = 46] received 0.2mg/kg; R2 group [n = 51] received 0.3mg/kg; and R3 group [n = 45] received 0.4mg/kg), or propofol (P group) received 2mg/kg. The successful induction of anesthesia defined efficacy without recall, the absence of rescue sedation with other sedatives, and the lack of additional medication dosages during the induction period. AEs, such as hypotension, established the safety endpoint.[22]

The results displayed that higher induction rates correlated with higher doses of remimazolam.[22] Remimazolam at a dose of 0.3-0.4mg/kg was comparable to Propofol induction rates ($p > 0.05$). At a lower dose of 0.2mg/kg, remimazolam had an induction success rate of 89%, requiring additional rescue medication. Therefore, R1 induction rate was observed to be lower than the P group ($p < 0.05$). [22] Upon induction, hypotension was found to be lower in R1 (13%) and R2 groups (24%) when compared to the p group (44%). Meanwhile, there was no significant difference in hypotension rates between R3 (34%) and the p group ($p \geq 0.05$).[22] Therefore, the study found that higher doses of remimazolam did increase hypotension rates. However, there were no serious AEs reported throughout the trial.[22] Based on the results, the

clinical trial concluded that remimazolam administered at high concentrations had an equivalent efficacy for induction as propofol. The authors concluded that remimazolam is a safe and effective induction drug with fewer adverse effects for general anes-thesia in ASA I and II patients.[22]

Non-Cardiac Elective Surgery

Hip Replacement. Claeys et al.[26] performed a Level II quasi-experimental study where they sought to investigate the hemodynamic effects of propofol when used for both induction and maintenance of anesthesia.[26] The results were then compared to those acquired in similar studies using other IV anesthetics such as althesin, methohexitone, and thiopentone. The study included ten adults 50-75 years of age rated ASA II-III and undergoing total hip replacement surgery under general anesthesia.[26] After baseline values were recorded, induction was initiated by administering patients with 2mg/kg over 30 seconds while concurrently starting a propofol infusion (n = 10) at a rate of 6mg/kg/hr lasting 60 minutes to maintain unconsciousness. Hemodynamic measurements were obtained at baseline, 2, 6, 10, 15, 20, 30, 45, and 60 minutes after the initial propofol administration.[26]

Statistical analysis found the mean values of HR, cardiac output (CO), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) changes were statistically inconsequential during all the collected times.[26] However, systemic arterial pressure (SAP) and diastolic arterial pressure (DAP) declined rapidly and significantly by 28% and 19%, respectively, immediately after the administration of the induction dose of propofol. During the maintenance stage, SAP and DAP decreased to 30% and 25%, respectively ($p < 0.001$).[26] Changes in blood pressure mirrored the decrease in systemic vascular resistance (SVR) on induction (-22%) and maintenance (-31%) ($p < 0.001$). Rate pressure product (RPP) remained

decreased during the entire trial. Stroke volume (SV) decreased minimally 2 minutes after induction and gradually returned to baseline values after that.[26] Upon comparison, the authors' results confirmed the hemodynamic effects of propofol during the induction and maintenance phase are comparable to those obtained in comparable studies where they used Althesin, minaxolone, methohexitone, and thiopentone as anesthesia agents.[26]

Cardiac Surgery

Coronary Artery Bypass. Singh et al.[8] performed a Level I experimental RCT where the study aimed to compare the hemodynamic impact of propofol, etomidate, thiopentone, and midazolam during anesthesia induction in patients with left ventricular dysfunction (LVD) and coronary artery disease (CAD).[8] Sixty patients suffering from CAD and LVD, with a cardiac ejection fraction of less than 45%, who were scheduled for elective coronary artery bypass (CABG) surgery were recruited for the study. The patients were randomly assigned to 1 of the 4 corresponding induction agents by the sealed envelope technique (n = 15 per group).[8] The intravenous induction agent was administered for over 60 to 90 seconds. Baseline hemodynamic data were recorded before induction and then at 1-minute intervals from induction until 7 minutes after intubation. Hemodynamic data recorded were then compared between the groups.[8]

After induction, there was a marked decrease from the baseline of p = 0.001 in each group in HR, MAP, CI, and SVI.[8] The study discovered that at an induction dose of 1.5mg/kg, patients in the propofol group demonstrated the most significant decrease from baseline with a MAP of -32%. These patients also had a reduction in additional hemodynamic variables such as heart rate (HR) of -10%, stroke volume index (SVI) of -29%, and systemic vascular resistance index (SVRI) of -9%.[8] Propofol also caused the most remarkable change in cardiac index (CI) of -38%. One patient in the propofol group required active volume resuscitation when the CI

decreased below 1.8 L/min/m2. The study concluded that each of the 4 anesthetic agents was acceptable for induction in patients with CAD and LVD despite a 30% to 40% decrease in the cardiac index.[8]

CABG, Valve, or Aortic. Hannam et al.[24] performed a Level I experimental RCT where the study aimed to compare the hemodynamic effects of etomidate and propofol as induction agents in cardiac surgical patients.[24] Patients were randomly chosen to be induced using either etomidate (n = 75) or propofol (n = 75). During the study's first phase (Phase I), patients were randomly selected to be induced with either anesthetic agent; however, the agent chosen was unblinded, also known as open-label.[24] During Phase II, the clinical and the study staff were blinded to the induction agent of choice. After induction, mean arterial blood pressure (MAP) and the use of vasopressors were documented for each group.[24] The primary endpoint was determined by the area under the curve (AUC), defined as the area under the baseline MAP within the 10min. after induction. The use of vasopressor drugs was assigned a numeric number (no bolus = 0, 1 or more boluses = 1) to then perform a logistic regression in which the results concluded as odds ratios (OR) with 95% confidence interval (CI).[24]

The findings resulted in the AUC (SD) for both blinded and unblinded for etomidate as -6595 (5404) mmHg s and -8839(5355) mmHg s for propofol.[24] The results lead to a mean difference of 2244 (95% CI, 581-3906) mmHg. This amount signifies a 34% (95% CI, 9-59%) more significant reduction with propofol, which is higher than the predefined level of clinical importance.[24] The study recorded 21/75 patients in the propofol group were given vasopressors during the first ten minutes after induction. Ten out of 75 patients in the etomidate group received pressors. These results provide an OR of 1.84 (95% CI, 0.47-7.27: P.0.38) in Phase I (open-label).[24] Due to the 34% greater reduction in AUC, the study concluded that propofol had

an inferior hemodynamic effect compared to etomidate. This result was clinically significant despite the more frequent use of vasopressors within the propofol group. The authors hypothesized that the increased use of vasopressors in the propofol group may have reduced the magnitude of its mean AUC of 34%.[24]

Valve Replacement. Liu et al.[9] performed a Level I experimental, double-blinded RCT where patients undergoing cardiac surgeries were randomly administered either remimazolam (*n* = 30) or propofol (*n* = 30) during induction of their general anesthesia.[9] The patient's hemodynamics during the induction process was then compared and evaluated. Patients that were scheduled for mitral valve replacement (MVR), atrial valve replacement (AVR), or double valve replacement (DVR) on cardiopulmonary bypass (CPB) that had a cardiac function graded as class II or III by the New York Heart Association and had a grade III by the American Society of Anesthesiologists (ASA) were included. Outcome measures for HR and MAP were collected by recording their value at baseline, 3 minutes after induction, directly before intubation (10 minutes after induction), and 1 minutes after intubation, and 5 minutes after intubation. The change in HR and MAP was the difference between their corresponding maximums and minimums to baseline.[9]

The study found the change in MAP was considerably more significant in the propofol group (▲MAP(mmHg)= 26.7 ± 9.1) compared to the remimazolam group (▲MAP (mmHg)= 19.5 ± 7.5) throughout induction.[9] The occurrence of hypotension and the average use of norepinephrine during induction was lower in the remimazolam group (Hypotension, *n* (%) = 5 (16.7%); Norepinephrine (ug)= 8.3 ± 18.9) than the propofol group (Hypotension, *n* (%) = 13 (43.3%); Norepinephrine (ug)= 33.3 ± 42.2). No substantial difference was found in changes in heart rate when both groups were compared. The study concluded that remimazolam was

effective and safe upon induction of general anesthesia and may be used as an alternative to propofol for patients undergoing valve replacement surgery.[9]

Tang et al.[10] performed a Level I experimental RCT where the investigators aimed to explore the clinical use of remimazolam benzenesulfonate in surgical cardiac patients undergoing general anesthesia.[10] The study implemented a random number table to divide 80 patients, classified ASA I—III, into 2 anesthesia induction groups. Group 1 (n = 40) patients were induced using remimazolam with a dose of 0.3 mg/kg, while Group 2 (n = 40) was induced using 1.5mg/kg of propofol.[10] Hemodynamic parameters such as MAP, HR, CI, and SVI, for the 2 groups were monitored during the pre-anesthesia (T0) induction, after endotracheal intubation (T1), at the time of sternal opening (T2), and the end of bypass use (T3).[10]

While the study did not find a significant difference in the hemodynamic variables during T0, it did find that T1 and T2 showed a significantly higher MAP (T1= 88.3 ± 4.7; T2= 86.7 ± 4.2) and SVI (T1= 43.80 ± 5.26; T2= 41.94 ± 5.57) in the remimazolam group than the propofol group (MAP: T1= 86.0 ± 4.4; T2= 83.8 ± 4.5) (SVI: T1= 40.38 ± 4.95; T2= 38.53 ± 4.86) ($P < 0.05$).[10] These results signified that remimazolam had a minimal effect on perioperative hemodynamics. The authors of the study hypothesized that the results reflected remimazolam's ability to act on adrenergic receptors, inhibit norepinephrine release, reduce the catecholamine level and sympathetic nerve excitability, and accelerate atrioventricular conduction, and hence improve myocardial contractility. The authors concluded that when compared to propofol, remimazolam benzenesulfonate aided cardiac surgical patients by diminishing hemodynamic fluctuations.[10]

Special Populations

ASA III or IV. Doi et al.[23] performed a Level I multicenter, double-blind, parallel-group trial, experimental RCT whose goal is to determine the safety and efficacy of remimazolam for induction of general anesthesia in high-risk surgical patients.[23] Patients included in the study must have been assigned an ASA of III or higher who were undergoing general anesthesia for surgery, were over 20 years old, and weighed less than 100 kg. A dynamic allocation was performed to randomly chose patients for both groups. Group A (n = 33) was induced using 6mg/kg/h of remimazolam. Group B (n = 34) was induced by 12mg/kg/h of remimazolam.[23] Both groups would receive an induction dose until LoC with safety endpoints established by the absence of adverse events (AE), such as a decrease in MAP. Efficacy was defined by the lack of clinical signs of awakening, which included ▲BP and ▲HR, successful induction of anesthesia without recall, the absence of rescue medication with other sedatives, and lack of body movement.[23]

The study found 100% efficacy for both remimazolam groups as a general anesthetic.[23] LoC was achieved for all patients observed, with the mean time for Group A being 97 seconds (p = 0.0139). Group B was considerably shorter, with a mean time of 82 seconds. Remimazolam induced LoC at mean (5–95%) with cumulative doses of 0.16 (0.11–0.24) mg/kg in group A and 0.27 (0.17–0.42) mg/kg in group B, respectively.[23] No statistically significant differences between both groups were found in the incidence of AE, as there was no hypotension reported or any other adverse events over the entire trial period or until the completion of intubation. The clinical trial successfully demonstrated the functional anesthetic capability of remimazolam for both groups.100% of the patients met clinical criteria because both groups reached LoC efficacy and safety endpoints without hemodynamic instability.[23]

Procedural Sedation

Gastrointestinal. Chen et al.[27] accomplished a Level I multicentered, blinded, active-controlled, non-inferior phase III RCT to appraise the safety and efficacy of remimazolam tosylate versus propofol in patients undergoing therapeutic or diagnostic colonoscopy.[27] Three hundred eighty-four patients were placed into a remimazolam (n = 196) or propofol (n = 192) group using a central randomization method. Patients who participated in the study were between 18 and 65 years old, with an ASA I-II and a BMI between 18-30kg/m^2.[27] Induction of sedation was achieved by administering either 5.0mg or 1.5mg/kg of propofol intravenously. The procedure was started when adequate sedation, defined by a Modified Observer's Assessment of Alertness/Sedation score (MOAA/S) score of ≤3 was achieved.[27] If sedation were insufficient after the initial dose, the patient would receive an additional dose of remimazolam 2.5mg/time or propofol 0.5mg/kg/time, respectively. Extra quantities were limited to a maximum of 5 doses in a 15 min window.[27] The efficacy endpoint was defined as the completion of the procedure without the administration of more than the maximum top-off allowance or administration of a rescue sedative. Safety endpoints included hypotension, which the study defined as the reduction of SBP of greater or equal to 20% when compared to baseline or an SBP ≤80 mmHg at any time during the procedure.[27]

The study resulted in a sedation success rate of 96.91% in the remimazolam group and 100% in the propofol group, with a difference in the rate of -3.09% confidence interval (CI) of -5.53% to approximately -0.66%.[27] The efficacy of remimazolam was categorized as non-inferior to propofol as the lower limit of 95% CI was more significant than the non-inferiority margin of -8%. Furthermore, the remimazolam group demonstrated significantly fewer rates of hypotension (23.71%) when compared to propofol (51.05%) ($p < 0.001$).[27] The trial concluded that the

sedation efficacy of the fast-acting benzodiazepine sedative agent, remimazolam tosylate, was non-inferior to propofol. Additionally, remimazolam proved much safer than propofol for patients undergoing colonoscopy.[27]

Discussion

The evidence obtained by the search of the literature validated the safety and efficacy of remimazolam in a multitude of different settings, populations, procedures, and anesthesia techniques. Although remimazolam is a novel medication, it has proven to have the same beneficial effects, such as hypnosis, sedation, and anti-anxiety, as other benzodiazepines. Additionally, remimazolam displays a similar fast-acting onset and short duration of action as propofol without being organ dependent for its metabolism. The extensive literature review highlighted remimazolam's non-inferior ability to induce patients for both general and procedural anesthesia with significantly diminished effects on hemodynamics, in particular blood pressure, when compared to propofol. Research has shown the importance of hemodynamic stability during the perioperative period and its possible detrimental postoperative effects on multiple organ functions, morbidity, and mortality. Therefore, with all the previously mentioned benefits of remimazolam, anesthesia providers can now choose an induction agent that may benefit patients not only intraoperatively but may decrease patient rates of postoperative morbidity and mortality.

Purpose and Objectives

Purpose

The research has shown that remimazolam has a superior hemodynamic profile and a comparable induction ability to propofol.[11] While propofol is still highly used for the induction of anesthesia, studies have repeatedly shown that it substantially reduces systemic and arterial

vascular resistance and may even reduce cardiac output. The repercussions of these effects have been linked to increased rates of postoperative mortality and morbidity.[5-7] Therefore, the primary goal of this Doctor of Nursing Practice (DNP) project was to construct and display an educational quality improvement module for anesthesia providers educating them regarding the novel drug remimazolam as an alternative to propofol for induction of anesthesia.

PICO Question

In interventional cardiovascular patients receiving monitored anesthesia care, would the use of remimazolam versus propofol decrease hemodynamic instability and reduce the risk of mortality and morbidity?

Population (P): Interventional cardiovascular patients

Intervention (I): Induction with remimazolam

Comparison (C): Induction with propofol

Outcomes (O): Effect on hemodynamics, defined by MAP or SBP

Goals and Outcomes

SMART Goals

To reach the objectives of a scholarly project such as this, there first needs to be a comprehensible, quantifiable, realistic, appropriate, and scheduled plan set in place. The SMART model was applied to direct the objectives and outcomes of this project in hopes of closing the knowledge gap and promoting possible quality improvement.

Specific. An evidence-based educational module was composed for anesthesia providers, discussing the current relationship between propofol's hemodynamic instability and increased

rates of postoperative mortality and how remimazolam may be a safer alternative for induction of anesthesia.

Measurable. To quantify the success of the quality improvement project, the author created a pre- and post-educational survey via a generated survey software called Qualtrics. The surveys were administered to the target audience, anesthesia providers from Miami Beach Anesthesiology Associates (MBAA). An overall improvement of 60% or higher from the pre- to post-assessment was defined as the acceptable benchmark for a successful project outcome.

Achievable. The quality improvement project was undoubtedly attainable as it required minimal resources for achievement. Additionally, anesthesia providers must stay up to date with current evidence-based practice and be educated on the basic pharmacokinetics and pharmacodynamics of propofol and other benzodiazepines like remimazolam. Armed with their basic knowledge in addition to an educational module explicitly composed for the targeted audience, the project's outcomes are attainable.

Relevant. Anesthesia providers aim to provide the utmost and safest care for their patients. Hypotension is a common and well-known side effect of several induction agents, especially propofol. Hemodynamic stability is a quintessential goal of any anesthesia provider during the perioperative period. Therefore, the information presented in this project was highly relevant to everyday clinical practice.

Time-based. The creation and implementation of the DNP project is part of a sequential construct that spanned approximately 12 months. The project was multifactorial and required approval at different stages from different stakeholders. Therefore, the approximation of a year is a realistic time frame.

Program Structure

As previously mentioned, the project was constructed sequentially with distinct stakeholders at each level. Therefore, the author applied the Plan, Do, Study, Act (PDSA) model for the proposed quality improvement project's structure and implementation design. The PDSA model is 1 of the most frequently used tools when implementing a quality improvement initiative.[28]

Plan

The author performed literary research during this project phase to conceptualize and plan the proposed change. Throughout the completed search and with the assistance of her faculty advisor, the author formulated a PICO question that would help guide and specify the evidence-based data needed to identify a problem, gain knowledge of the extent of the problem, and investigate potential interventions during an in-depth literature review.

Do

In the Do phase, the information gained from the literature review was used to develop the project's specific purpose, goals, and outcomes. It was during this phase that SMART goals were established. The project's goal was made clear and precise, measurable outcomes were defined, realistic expectations were formulated, the intervention was confirmed as relevant, and a target time for project completion was established. Throughout the do phase, specific organizational factors of the program's implementation process were identified. For example, factors such as roles and responsibilities, tasks to be completed, the required technology, available resources, and possible barriers to implementing interventions. Additionally, an organizational assessment identified the project's strengths, weaknesses, opportunities, and threats (SWOT).

Study

Through the Study phase, the project proposed to implement a pre-assessment survey to study the current gaps in knowledge regarding its subject matter. More importantly, the pre-assessment tool may provide essential information regarding the anesthesia providers' views regarding the problem, institutional willingness to introduce change, and identify possible barriers that may arise throughout the implementation process. An audience-specific educational module may be created and implemented with the information gained. Once the quality improvement educational module was presented, the post-assessment tool evaluated progress against the defined outcome goal criteria.

Act

The Act phase was one of reflection. The quality improvement project was re-assessed for its strengths and failures. At this point, adjustments to goals, methods, and interventions may be made in hopes that the intervention proposed in the educational module will 1 day improve the patients' quality of care.

Organizational Factors

The development and implementation of this DNP project was conducted under the guidance of an interdisciplinary team. The author's faculty advisor guided the project's structure and was the liaison between the author and Florida International University's (FIU) Alumni members. The author's clinical preceptor was a mentor in the clinical setting and was responsible for guiding the structure of the pre- and post-assessment survey. FIU's Department of Nurse Anesthesiology alumni members were the focused population for the designated intervention. They viewed the completed educational module and complete the pre- and post-evaluation survey.

Resources and fiduciary costs for the project were minimal, as the author was the project's primary investigator. Similarly, the partaking alumni members donated their time to participate in the implementation of the project. This ensured organizational daily workflow is undisturbed and therefore comes at no cost to any individual institution. Lastly, and as previously mentioned, the author used the services of Qualtrics for the development of the pre- and post-assessment tools.

Figure 1. SWOT Analysis

Methodology

Setting and Participants

The setting for the DNP project was multi-organizational, as the members within FIU's alumni group are anesthesia provides who practice in different locations all over the United

States. Approval through the International Review Board (IRB) was requested for the implementation of the project. Voluntary anesthesia providers were asked to provide their email addresses to access the educational module and pre- and post-assessment survey links. All participants remained anonymous throughout the entirety of the project.

Approach and Project Procedures

The primary goal of the intended project was to educate anesthesia providers regarding the hemodynamic instability of propofol and possible postoperative effects linked to perioperative hypotension. Additionally, the education module introduced remimazolam as a more hemodynamically stable alternative for induction of anesthesia. The enhancement, creation, and dissemination of knowledge followed a timeline and adhere to standard protocols. After submission and approval by Florida International University (FIU) and the IRB, the quality improvement project was presented to FIU alumni. An individualized and nontransferable link was sent to the participants via email. The link provided the pre-assessment survey for completion.

The education module was created by first assessing the anesthesia providers' current knowledge regarding propofol's intraoperative hemodynamic instability, the link to postoperative complications, and information regarding remimazolam and its possible benefits. The pre-assessment also included a section addressing potential barriers to the quality improvement project and assessed the participants' willingness to accept change in customary clinical practice. Using this data and evidence-based articles, the author developed an educational module specific to the participants' knowledge gaps. Upon completing an education voiceover PowerPoint presentation, the participants can access the module and post-assessment

survey via the emailed link. The author addressed questions and concerns and provided contact information for future communication if needed.

Protection of Human Subjects

All participants were contacted via email. Participation was strictly anonymous and entirely voluntary. The personal identifiers of the participants were not collected nor stored. Participation consent was obtained. All survey responses remained nameless, protecting the privacy of the participants. Only minimal risks were associated with the QI project, including the requirement of anesthesia providers to sacrifice 15-20 minutes of their time to complete the education module and tests.

Data Collection

After consent was obtained from the participating anesthesia providers, they accessed a link to the pre-assessment survey, where they were asked to provide voluntary demographic information such as ethnicity, gender, race, and level of education. The pre- and post-assessment surveys were generated and dispersed via Qualtrics, and the information obtained was exported into an Excel file for comparison. A total average of all the correct answered questions for each survey was obtained and mathematically formulated into a percentage for comparison. An overall improvement of 20% or higher from the pre- to post-assessment, or an average of 85% or higher in the post-assessment survey, was the acceptable benchmark for a successful project outcome.

Data Management/Analysis

The Qualtrics database was password protected, with accessibility only provided to the private investigator and associates. Participant identifiers were not collected or associated with

any entered data or analysis. Comparative analysis through Microsoft's Excel software assisted in calculating the data results.

Results

Sample Size and Demographics

Fourteen anesthesia providers consented to participate in the study (n = 14). The complete cohort of 14 participants successfully engaged with the educational module and fulfilled the requirements of the pre-assessment tool. However, in the subsequent stage, only 11 participants completed the post-assessment survey (n = 11). Consequently, 3 participants were deemed ineligible for inclusion in the project and its subsequent analysis, resulting in a final sample size of 11 (n = 11) participants for the conclusive investigation.

The demographic characteristics of the participants are delineated in Table 1. Out of the 11 anesthesia providers who took part, 7 self-identified as male, constituting 63.64% of the sample, whereas 4 self-identified as female, comprising 36.36%. The participants' ages ranged from 20 to 48, with an average age of 34. Moreover, the group exhibited a diverse representation of ethnicities, with 5 participants identifying as Caucasian (45.45%), 3 as African American (27.27%), 2 as Hispanic (18.18%), and 1 as Asian (9.09%). All individuals who participated held a Doctor of Nursing Practice Degree (DNP) and were Certified Registered Nurse Anesthetists (CRNAs), encompassing the entirety of the sample (n = 11, 100%). Concerning anesthesia practice experience, most participants had less than 2 years of experience with 5 participants (45.45%) possessing 1-2 years of experience, while another 5 (45.45%) having between 2-5 years. Lastly, 1 participant (9.09%) boasted over 10 years of experience.

Table 1. Participants' Demographics

Participants (*N* = 11)	**Number (*N*)**	**%**
Gender		
Male	7	63.64%
Female	4	36.36%
Ethnicity		
Caucasian	5	45.45%
African American	3	27.27%
Hispanic	2	18.18%
Asian	1	9.09%
Other	0	0.00%
Position		
CRNA	11	100%
Level of Education		
MSN	0	0.00%
DNP	11	100%
Years of Experience		
0-1	5	45.45%
1-2	5	45.45%
2-5	0	0.00%
5-10	0	0.00%
Over 10 years	1	9.09%

Pretest Knowledge of Remimazolam and Propofol

The anesthesia providers were given a pre-assessment evaluation to assess their existing knowledge of propofol's and remimazolam's hemodynamic profiles, common postprocedural complications, and their willingness to change customary clinical practice. The pre-assessment questions are shown in Table 2. While most of the providers were knowledgeable regarding common causes of postoperative morbidity and mortality and benefits of remimazolam, they lacked awareness of remimazolam's mechanisms of action and favorable hemodynamic stability.

Table 2. Pre- and Post-Survey Responses

Questions	**Pretest**	**Posttest**	**Change**
1. What is the leading cause of postoperative/postprocedural deaths?	*N* (%)	*N* (%)	%
Kidney Failure	2 (18.18)	0 (0.00)	18.18↓
Myocardial Infarction*	8 (72.73)	9 (81.82)	9.09↑
Sepsis	1 (9.09)	2 (18.18)	9.09↑
Pulmonary Embolism	0 (0.00)	0 (0.00)	0.00
2. Hypotension is strongly associated with which postprocedural complication?			
Myocardial Infarction	1 (9.09)	0 (0.00)	9.09↓
Acute Kidney Failure	2 (18.18)	0 (0.00)	18.18↓
Death	0 (0.00)	1 (9.09)	9.09↑
All the above*	8 (72.73)	10 (90.91)	18.18↑
3. Risk of postprocedural mortality is markedly increased when:			
MAP≤60 mmHg for 15 min.	7 (63.64)	1 (9.09)	54.55↓
MAP≤65 mmHg for 20 min.	4 (36.36)	0 (0.00)	36.36↓
MAP≤70 mmHg for 15 min.	0 (0.00)	2 (18.18)	18.18↑
MAP≤70 mmHg for 10 min.*	0 (0.00)	8 (72.73)	72.73↑
4. Propofol is the medication of choice for the induction of anesthesia because:			
Fast-acting onset and short duration of action*	4 (36.36)	6 (54.55)	18.19↑
Safest induction medication on the market with the least adverse effects	0 (0.00)	0 (0.00)	0.00
Long duration of action	0 (0.00)	1 (9.09)	9.09↑
Both A and B	7 (63.64)	4 (36.36)	27.28↓
5. Propofol has been known to substantially decrease which hemodynamic variable?			
MAP	2 (18.18)	0 (0.00)	0.00
Cardiac Output	0 (0.00)	0 (0.00)	0.00
Systemic Vascular Resistance	2 (18.18)	1 (9.09)	9.09↓
All the above*	7 (63.64)	10 (90.91)	27.27↑
6. Remimazolam is a new FDA approved benzodiazepine with a promising combination of advantages of both:			
Fentanyl and Midazolam	6 (54.55)	0 (0.00)	54.55↓
Midazolam and Propofol*	4 (36.36)	11 (100.00)	63.64↑

Propofol and Fentanyl	0 (0.00)	0 (0.00)	0.00
Ketamine and Propofol	1 (9.09)	0 (0.00)	9.09↓
7. What are some of the benefits of using remimazolam over propofol for induction?			
Fewer cardio-depressant effects	1 (9.09)	0 (0.00)	9.09↓
Inactive metabolite via esterase activity	0 (0.00)	0 (0.00)	0.00
Similar fast-active onset and short duration of action	0 (0.00)	1 (9.09)	9.09 ↑
All the above*	10 (90.91)	10 (90.91)	0.00
8. Remimazolam has been proven to be a safe and effective alternative to propofol during the induction of anesthesia for which procedure?			
Outpatient procedures such as colonoscopies	1 (9.09)	0 (0.00)	9.09↓
Minor examinations such as bronchoscopies	2 (18.18)	0 (0.00)	18.18↓
General surgery	0 (0.00)	1 (9.09)	9.09 ↑
All the above*	8 (72.73)	10 (90.91)	18.18↑
9. Propofol has a superior hemodynamic profile compared to remimazolam.			
True	1 (9.09)	2 (18.18)	9.09 ↑
False*	10 (90.91)	9 (81.82)	9.09↓
10. If available to you, how likely are you to utilize remimazolam as an alternative to propofol during the induction of monitored anesthesia care			
Extremely unlikely	1 (9.09)	0 (0.00)	9.09↓
Somewhat unlikely	1 (9.09)	2 (18.18)	9.09 ↑
Neither likely nor unlikely	6 (54.55)	0 (0.00)	54.55↓
Somewhat likely	2 (18.18)	4 (36.36)	18.18↑
Extremely likely	1 (9.09)	5 (45.45)	36.36↑

*Correct Answer.

The participants in the study were tasked with identifying the primary cause of postoperative and postprocedural deaths. Among the respondents, 3 providers answered incorrectly. Two of them (*n* = 2, 18.18%) incorrectly identified "kidney failure" as the leading cause, while the other 1 (*n* = 1, 9.09%) answered "sepsis." In contrast, 8 anesthesia providers (*n* = 8, 72.73%) responded correctly, recognizing "myocardial infarction" as the leading cause of postoperative deaths. When asked about the postprocedural complication strongly associated with hypotension, 1 provider (*n* = 1, 9.09%) erroneously chose "myocardial infarction" as the

answer, while 2 providers (*n* = 2, 18.18%) incorrectly selected "acute kidney failure." In contrast, 8 participants correctly identified "All of the above" as the answer, encompassing myocardial infarction, acute kidney failure, and death. Interestingly, when the anesthesia providers were asked to correlate mean arterial pressure (MAP) values with the duration of time that significantly increases postprocedural mortality, none of them (*n* = 0, 0.00%) chose the correct answer, which is "MAP ≤ 70 mmHg for 10 minutes." Seven participants (*n* = 7, 63.64%) incorrectly answered "MAP ≤ 60 mmHg for 15 minutes," while 4 (*n* = 4, 36.36%) inaccurately responded with "MAP ≤ 65 mmHg for 20 minutes."

While most anesthesia providers know propofol is the preferred drug for anesthesia induction, participants were asked to explain why. Seven providers (*n* = 7, 63.64%) answered incorrectly by selecting "Both A and B," which included the options "Fast-acting onset and short duration of action" and "Safest induction medication on the market with the least adverse effects." Four providers (*n* = 4, 36.36%) answered correctly, indicating that the only accurate choice is "Fast-acting onset and short duration of action." When asked about the specific hemodynamic variables affected by the administration of propofol, 2 providers (*n* = 2, 18.18%) responded incorrectly by selecting "MAP," while another 2 (*n* = 2, 18.18%) inaccurately chose "Systemic Vascular Resistance." The remaining participants (*n* = 7, 63.64%) responded appropriately by selecting "all of the above," encompassing MAP, cardiac output, and systemic vascular resistance.

Subsequently, the anesthesia providers were tested on their knowledge of the newly FDA-approved drug remimazolam. They were asked to identify the medications to which remimazolam's promising benefits are compared. Only 4 participants (*n* = 4, 36.36%) accurately responded with "midazolam and propofol." Six participants (*n* = 6, 54.55%) chose "fentanyl and

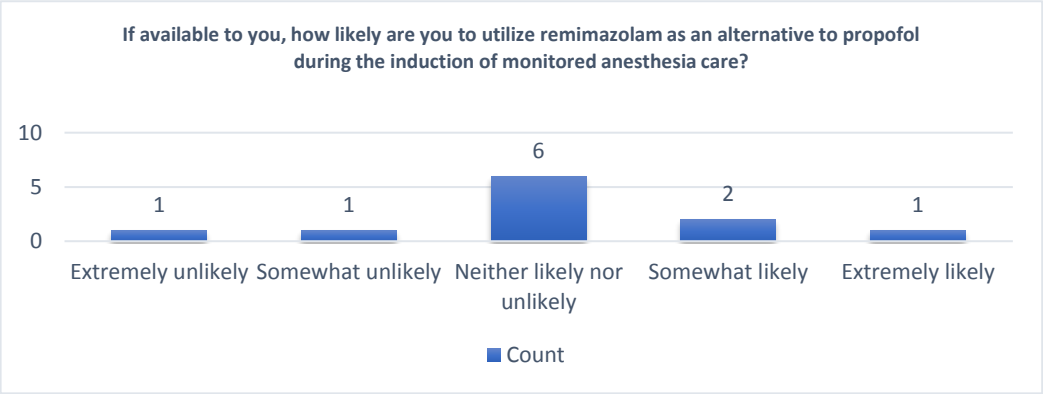
midazolam," and 1 participant (*n* = 1, 9.09%) selected "ketamine and propofol" incorrectly. When asked about the benefits of using remimazolam over propofol for induction, 10 providers (*n* = 10, 90.91%) responded appropriately by selecting "all of the above." These benefits included fewer cardio-depressant effects, inactive metabolite via esterase activity, and a similar fast-acting onset and short duration of action as propofol. One participant selected "fewer cardio-depressant effects" incorrectly.

The anesthesia providers were then asked about the procedures for which remimazolam has been proven to be a safe and effective alternative to propofol for anesthesia induction. One participant (*n* = 1, 9.09%) and an additional 2 participants (*n* = 2, 18.18%) responded erroneously by selecting "Outpatient procedures such as colonoscopies" and "Minor examinations such as bronchoscopies," respectively. Eight providers (*n* = 8, 72.73%) correctly chose "All of the above," which included outpatient procedures such as colonoscopies, minor examinations such as bronchoscopies, and general surgery. Moreover, the participants were asked if propofol has a superior hemodynamic profile compared to remimazolam. Ten providers (*n* = 10, 90.91%) answered appropriately with "False," while 1 participant (*n* = 1, 9.09%) incorrectly answered "True."

To gauge the current attitudes related to remimazolam over propofol for anesthesia induction, providers were asked about their likelihood of utilizing remimazolam as an alternative if available to them during monitored anesthesia care (MAC) induction. As depicted in Figure 1, most anesthesia providers (*n* = 6, 54.55%) expressed ambivalence toward utilizing remimazolam. Two participants (*n* = 2, 18.18%) were "somewhat likely," while another participant (*n* = 1, 9.09%) was "extremely likely." On the contrary, 1 provider (*n* = 1, 9.09%) expressed being

"extremely unlikely" to choose remimazolam over propofol, and another provider (*n* = 1, 9.09%) was somewhat unlikely to do so.

Figure 2. Pre-Assessment Survey Results Q10



Posttest Knowledge of Remimazolam and Propofol

After completing the pre-assessment survey, the participants were granted access to an educational module in the form of a PowerPoint presentation. This module provided comprehensive information regarding the effects of intraoperative hypotension on postoperative mortality and morbidity rates, as well as the impact of both propofol and remimazolam on patients' hemodynamics in various clinical settings. Upon reviewing the module, the participants were presented with a post-assessment survey containing the same questions as the pre-assessment survey. The questions and corresponding results of the post-assessment survey are shown in Table 2.

When asked again to identify the leading cause of postoperative/postprocedural deaths, 2 providers (*n* = 2, 18.18%) responded incorrectly by selecting "sepsis." However, more anesthesia providers, precisely 9 (*n* = 9, 81.82%), correctly identified "myocardial infarction" as the leading cause of postoperative deaths. There was a 9.09% increase in the selection of "myocardial infarction" as the correct answer in the post-assessment compared to the pre-assessment.

Similarly, when queried again about the postprocedural complication strongly associated with hypotension, there was an 18.18% increase in the correct response selection compared to the pre-assessment. During this assessment, 10 providers (*n* = 10, 90.91%) appropriately answered with "All the above," while only 1 participant (*n* = 1, 9.09%) responded incorrectly by selecting "Death." Upon reassessment regarding the risk at which postprocedural mortality is significantly increased, there was a substantial surge of 72.73% (*n* = 8) of participants selecting the correct answer of "MAP ≤ 70 mmHg for 10 minutes" compared to the pre-assessment, where all participants answered incorrectly. The remaining participants responded inaccurately, with 2 (*n* = 2, 18.18%) selecting "MAP ≤ 70 mmHg for 15 minutes" and 1 (*n* = 1, 9.09%) choosing "MAP ≤ 60 mmHg for 15 minutes."

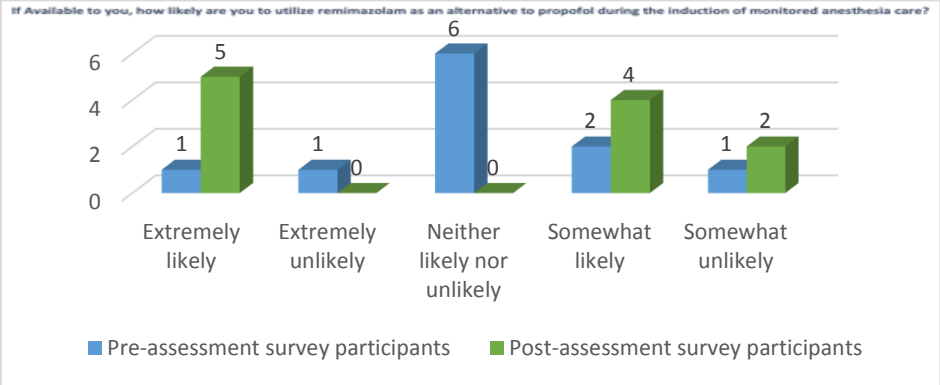
The anesthesia providers were then reevaluated regarding why propofol is the preferred medication for the induction of anesthesia. Four providers (*n* = 4, 36.36%) answered incorrectly by selecting "Both A and B," and another provider (*n* = 1, 9.09%) made the same mistake by choosing "Long duration of action." Six providers (*n* = 6, 54.55%) correctly indicated that "Fast-acting onset and short duration of action" is the only accurate choice. This resulted in an 18.19% (*n* = 2) increase in the percentage of correct answers after completing the educational module. When asked again about the specific hemodynamic variables affected by the administration of propofol, 1 provider (*n* = 1, 9.09%) inaccurately chose "Systemic Vascular Resistance," while the remaining participants (*n* = 10, 90.91%) responded appropriately by selecting "All the above." This resulted in a 27.27% (*n* = 3) increase after completing the educational module.

The anesthesia providers were then retested on their acquired knowledge of remimazolam. They were again asked to identify the medications to which remimazolam is compared. After completing the educational module, all participants (*n* = 11, 100.00%)

responded correctly by selecting "midazolam and propofol." This represented a 63.64% (*n* = 7) increase in knowledge. However, there was no significant change in the participants' responses regarding the benefits of using remimazolam over propofol for induction. Ten providers (*n* = 10, 90.91%) continued to respond appropriately by selecting "All the above," while 1 participant (*n* = 1, 9.09%) still answered incorrectly with "Similar fast-active onset and short duration of action." When reassessed regarding the procedures for which remimazolam has been proven to be a safe and effective alternative to propofol for anesthesia induction, 1 participant (*n* = 1, 9.09%) erroneously chose "general surgery." However, 10 providers (*n* = 10, 90.91%) correctly chose "All the above," resulting in an 18.18% (*n* = 2) increase between the pre-assessment and post-assessment surveys. Conversely, when participants were once again questioned whether propofol has a superior hemodynamic profile compared to remimazolam, there was a 9.09% (*n* = 1) decrease in the number of participants selecting the correct answer of "False." This was due to 2 participants (*n* = 2, 18.18%) incorrectly choosing "True," while the remaining 9 participants (*n* = 9, 81.82%) responded appropriately.

Lastly, when participants were once again asked about their likelihood of utilizing remimazolam as an alternative to propofol during the induction of monitored anesthesia care (MAC), the results showed less ambiguity than the pre-assessment survey. Two anesthesia providers (*n* = 2, 18.18%) expressed being "somewhat unlikely" to choose remimazolam, while 4 providers (*n* = 4, 36.26%) were "somewhat likely," and 5 providers (*n* = 5, 45.45%) were "extremely likely." Figure 3 displays the comparative results of the pre-assessment and post-assessment surveys for Question 10.

Figure 3. Pre- and Post-Assessment Survey Results Q10



Upon the completion of data collection, the collected data points were analyzed by calculating the average of correct answers for both the pre-assessment and post-assessment surveys. This analysis aimed to assess the extent of learning enhancement achieved as a result of the educational module and determine the project's overall success. Each question had a maximum possible score of 11, representing the 11 participants involved in the study. For question number 10, which did not have a right or wrong answer, 11 points were awarded for the pre- and post-assessments.

Predetermined benchmarks were established to evaluate the project's success and quantify the knowledge acquired through the educational module. Specifically, a 20% increase in the average of correct answers chosen from the pre- to post-knowledge test or an overall average of 85% in the post-knowledge test was considered indicative of project success. The analysis revealed that the average percentage of correct responses on the pre-assessment survey was 63.6%, while the post-assessment survey yielded an average of 85.5% correct responses. These findings demonstrate a substantial increase in knowledge of 21.9% following the participants' exposure to the educational module.

Discussion

Limitations

Utilizing a pre- and post-assessment survey for a DNP project has certain limitations that should be acknowledged. Firstly, using alum students as the sole participant pool introduces potential selection bias and a modest sample size. This approach may limit the generalizability of the findings since the alum population may not accurately represent the wider anesthesia community. The results may be influenced by the participants' specific experiences, interests, and motivations, which may differ from those of current students or practicing anesthesia providers. Therefore, caution should be exercised when extrapolating the findings to a broader context.

Furthermore, the exclusive use of an online platform to distribute the pre- and post-assessment survey and the accompanying educational module may introduce biases related to technology access and proficiency. By limiting the survey distribution to an online platform, the project may inadvertently exclude individuals who lack internet access or who are not technologically inclined. This limitation can lead to a biased sample, potentially omitting individuals from certain demographic or geographic groups. Additionally, the reliance on an online platform may affect the alum population's response rate and representativeness. Those who are less comfortable with online interactions or have limited access to the platform may be less likely to participate, further skewing the results.

Future Implications

Research findings demonstrate that remimazolam offers improved controllability and exerts fewer effects on the cardiorespiratory system. This pharmacological agent holds remarkable advantages in the realm of clinical sedation, as it exhibits versatility in its

applicability across diverse patient populations. In addition to its established role as an induction medication, remimazolam shows promise as an adjuvant sedative agent for various procedures performed under local anesthesia, cardiac interventional procedures, and in patients with specific characteristics such as advanced age, obesity, and ASA III and IV classifications.

Given the significance of maintaining hemodynamic stability during the perioperative period and the potentially harmful impact on multiple organ functions, morbidity, and mortality in the postoperative phase, choosing an appropriate induction agent becomes paramount for anesthesia providers. With the availability of remimazolam, these providers now have the option to select an induction agent that not only offers a superior hemodynamic profile but also holds the potential to mitigate postoperative morbidity and mortality.

Conclusion

The extensive literature review conducted for this DNP project underscored the non-inferiority of remimazolam as an induction agent for both general and procedural anesthesia, exhibiting significantly reduced impact on hemodynamics, particularly blood pressure, compared to propofol. The importance of maintaining hemodynamic stability during the perioperative period and the potential adverse effects on multiple organ functions, morbidity, and mortality associated with hemodynamic instability were highlighted. Research consistently demonstrated that remimazolam possesses a superior hemodynamic profile while exhibiting comparable induction efficacy to propofol.

The primary objective of this DNP project was to develop and present an educational quality improvement module for anesthesia providers, focusing on educating them about the innovative drug remimazolam as a viable alternative to propofol for the induction of monitored

anesthesia care. The analysis of both the pre- and post-assessment surveys determined that the project successfully met its predetermined benchmarks. The observed improvement in learning outcomes confirms the positive impact of the educational intervention, enhancing participants' understanding and retention of the material. These results provide compelling evidence supporting the project's success in facilitating learning and promoting the acquisition of knowledge among anesthesia providers. By disseminating knowledge about remimazolam and its potential benefits, this project contributes to advancing evidence-based practice and optimizing patient care during the induction of monitored anesthesia care.

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Appendices

Appendix A: Letter of Support

FIU
Department of Nurse Anesthesiology

Nicole Wertheim College of Nursing & Health Sciences

February 7, 2023

Yasmine Campbell, DNP, CRNA, APRN
Clinical Assistant Professor
Department of Nurse Anesthesiology
Florida International University

Dr. Campbell,

Thank you for inviting FIU alumni to participate in the Doctor of Nursing Practice (DNP) project conducted by Leidy Escobar entitled "Remimazolam as an alternative induction agent in monitored anesthesia care, an educational module" in the Nicole Wertheim College of Nursing and Health Sciences, Department of Nurse Anesthesiology at Florida International University. I have granted the student permission to conduct the project using our providers.

Evidence-based practice's primary aim is to yield the best outcomes for patients by selecting interventions supported by the evidence. This proposed quality improvement project seeks to utilize the latest literature to increase providers' awareness regarding the use of remimazolam as an alternate induction agent in monitored anesthesia care.

We understand that participation in the study is voluntary and carries no overt risk. All Anesthesiology providers are free to participate or withdraw from the study at anytime. The educational intervention will be conveyed by a 10-minute virtual PowerPoint presentation, with a pretest and posttest questionnaire delivered by a URL link electronically via Qualtrics, an online survey product. Responses to pretest and posttest surveys are not linked to any participant. The collected information is reported as an aggregate, and there is no monetary compensation for participation. All collected material will be kept confidential, stored in a password-encrypted digital cloud, and only be accessible to the investigators of this study: Leidy Escobar and Dr. Yasmine Campbell.

Once the Institutional Review Board's approval is achieved, this scholarly project's execution will occur over two weeks. Leidy Escobar will behave professionally, follow standards of care, and not impede hospital performance. We support the participation of our Anesthesiology providers in this project and look forward to working with you.

Sincerely,

Jorge A. Valdes, DNP, CRNA, APRN, FAANA
Chair, Department of Nurse Anesthesiology
Associate Professor

Appendix B: IRB Approval Letter

FIU | Research & Economic Development
FLORIDA INTERNATIONAL UNIVERSITY

MEMORANDUM

To:	Dr. Yasmine Campbell
CC:	Leidy Escobar
From:	Carrie Bassols, BA, IRB Coordinator CeB
Date:	March 2, 2023
Proposal Title:	"Remimazolam as an Alternative Induction Agent in Monitored Anesthesia Care, an Educational Module."

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #:	IRB-23-0080	**IRB Exemption Date:**	03/02/23
TOPAZ Reference #:	112772		

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
1) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

Appendix C: Invitation to Participants

FIU Department of Nurse Anesthesiology

Nicole Wertheim College of Nursing & Health Sciences

Remimazolam as Alternative Induction Agent in Monitored Care Anesthesia, an Educational Module.

Dear FIU Alumni Perioperative Providers:

My name is Leidy Escobar, and I am a student from the Anesthesiology Nursing Program Department of Nurse Anesthesiology at Florida International University. I am writing to invite you to participate in my quality improvement project. The goal of this project is to increase health care providers' awareness on the use of remimazolam as an alternate induction agent in monitored anesthesia care. You are eligible to take part in this project because you are a part of the FIU Alumni perioperative provider.

If you decide to participate in this project, you will be asked to complete and sign a consent form for participation. Next, you will complete a pre-test questionnaire, which is expected to take approximately 5 minutes. You will then be asked to view an approximately 10 minutes long educational presentation online. After going through the educational module, you will be asked to complete the post-test questionnaire, which is expected to take approximately 5 minutes. No compensation will be provided.

Remember, this is completely voluntary. You can choose to be in the study or not. If you'd like to participate or have any questions about the study, please email or contact me at (786) 436-1231/lesco003@fiu.edu.

Thank you very much.

Sincerely,

Leidy Escobar

(786) 436-1231

Lesco003@fiu.edu

Appendix D: Informed Consent

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CONSENT TO PARTICIPATE IN A QUALITY IMPROVEMENT PROJECT

Remimazolam as an Alternative Induction Agent in Monitored Anesthesia Care, an Educational Module.

SUMMARY INFORMATION
Things you should know about this study:

- **Purpose**: Educational module to increase providers awareness of the use of remimazolam as an alternate induction agent in monitored anesthesia care.
- **Procedures**: If the participant chooses to participate, they will be asked to complete a pretest, watch a voice PowerPoint, and then a post test
- **Duration**: This will take about a total of 20 minutes total.
- **Risks**: There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may include mild emotional stress or mild physical discomfort from sitting on a chair for an extended period.
- **Benefits**: The main benefit to you from this research is increase the participants knowledge on the use of remimazolam as an alternate induction agent in monitored anesthesia care.
- **Alternatives**: There are no known alternatives available to the participant other than not taking part in this quality improvement project.
- **Participation**: Taking part in this quality improvement project is voluntary.

Please carefully read the entire document before agreeing to participate.

NUMBER OF STUDY PARTICIPANTS:

If the participant decides to be in this study, they will be one of ten people in this research study.

PURPOSE OF THE PROJECT

The participant is being asked to be in a quality improvement project. The goal of this project is to increase providers' knowledge on the use of remimazolam as an alternate induction agent in monitored anesthesia care. If you decide to participate, you will be 1 of approximately 10 participants.

DURATION OF THE PROJECT
The participation will require about 20 minutes

PROCEDURES
If the participant agrees to be in the project, PI will ask you to do the following things:
1. Complete an online 10 question pre-test survey via Qualtrics, an Online survey product for which the URL link is provided
2. Review the educational PowerPoint Module lasting 10 minutes via Qualtrics, an Online survey product for which the URL link is provided.
3. Complete the online 10 question post-test survey via Qualtrics, an Online survey product for which the

URL link is provided.

RISKS AND/OR DISCOMFORTS
The main risk or discomfort from this research is minimal. There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may include mild emotional stress or mild physical discomfort from sitting on a chair for an extended period.

BENEFITS

- The following benefits may be associated with participation in this project: Gaining knowledge regarding remimazolam as an alternate induction agent in monitored anesthesia care. The overall objective of the program is to increase the providers' knowledge based on the current literature.

ALTERNATIVES
There are no known alternatives available to the participant other than not taking part in this project. However, if the participant would like to receive the educational material, it will be provided to them at no cost.

CONFIDENTIALITY
The records of this project will be kept private and will be protected to the fullest extent provided by law. If, in any sort of report, PI might publish, it will not include any information that will make it possible to identify the participant. Records will be stored securely, and only the project team will have access to the records.

PARTICIPATION: Taking part in this quality improvement project is voluntary.

COMPENSATION & COSTS
There is no cost or payment to the participant for receiving the health education and/or for participating in this project.

RIGHT TO DECLINE OR WITHDRAW
The participation in this project is voluntary. The participant is free to participate in the project or withdraw the consent at any time during the project. The participant's withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove the participant without their consent at such time that they feel it is in their best interest.

RESEARCHER CONTACT INFORMATION
If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Leidy Escobar at (786) 436-123/lesco003@fiu.edu, and Dr. Yasmine Campbell at (305) 348-9894/ycambel@fiu.edu.

IRB CONTACT INFORMATION
If the participant would like to talk with someone about their rights pertaining to being a subject in this project or about ethical issues with this project, the participant may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by email at ori@fiu.edu.

PARTICIPANT AGREEMENT

I have read the information in this consent form and agree to participate in this study. I have had a chance to ask any questions I have about this study, and they have been answered for me. By clicking on the "consent to participate" button below I am providing my informed consent.

Appendix E: Data Collection Instrument (Pre- and Post-Survey)

Pretest and Posttest Questionnaire:

Remimazolam as Alternative Induction Agent in Monitored Anesthesia Care an Educational Module.

INTRODUCTION

The primary aim of this QI project is to increase providers awareness of the use of remimazolam as an alternate induction agent in monitored anesthesia care.

Please answer the question below to the best of your ability. The questions are either in multiple choice or true/false format and are meant to measure knowledge on the use of remimazolam as an alternate induction agent in monitored anesthesia care.

PERSONAL INFORMATION

1. **Gender:** Male Female Other_____
2. **Ages 25 and above:** _____
3. **Ethnicity:** Hispanic Caucasian African American Asian Other_____
4. **Position/Title:** CRNA Anesthesiologist Resident Anesthesiologist Assistant
5. **Level of Education:** Certificate Bachelors Masters DNP PhD
6. How many years have you been a perioperative provider?

   Over 10 5-10 years 2-5 years 1-2 years

QUESTIONNAIRE

1. **What is the leading cause of postoperative/postprocedural deaths?**
    a. Kidney Failure
    b. Myocardial Infarction
    c. Sepsis
    d. Pulmonary Embolism
2. **Hypotension is strongly associated with which postprocedural complication:**
    a. Myocardial infarction
    b. Acute kidney injury
    c. Death
    d. All the above
3. **Risk of postprocedural mortality is markedly increased when:**
    a. MAP ≤60 mmHg for 15 minutes
    b. MAP ≤65 mmHg for 20 minutes
    c. MAP ≤ 70 mm Hg for 15 minutes
    d. MAP≤70 mmHg for 10 minutes
4. Propofol is the medication of choice for the induction of anesthesia because
    a. Fast-acting onset and short duration of action
    b. Safest induction medication on the market with the least adverse effects
    c. Both A and B
    d. None of the above
5. **Propofol has been known to substantially decrease which hemodynamic variable?**
    a. MAP

b. Cardiac Output

c. Systemic Vascular Resistance

d. All the above

6. **Remimazolam is a new FDA approved Benzodiazepine with a promising combination of advantages of both:**

   a. Fentanyl and Midazolam

   b. Midazolam and Propofol

   c. Propofol and Fentanyl

   d. Ketamine and Propofol

7. **What are some of the benefits of using Remimazolam over Propofol for induction?**

   a. Fewer cardio-depressant effects

   b. Inactive metabolite via esterase activity

   c. Similar fast-active onset and short duration of action

   d. All the above

8. **Remimazolam has been proven to be a safe and effective alternative to Propofol during the induction of anesthesia for which procedure?**

   a. Outpatient procedures such as colonoscopies

   b. Minor examinations such as bronchoscopies

   c. General surgery

   d. All the above

9. **Propofol has a superior hemodynamic profile compared to Remimazolam?** True or False

10. **How likely are you to utilize remimazolam as an alternative to propofol during the induction of monitored care anesthesia?**

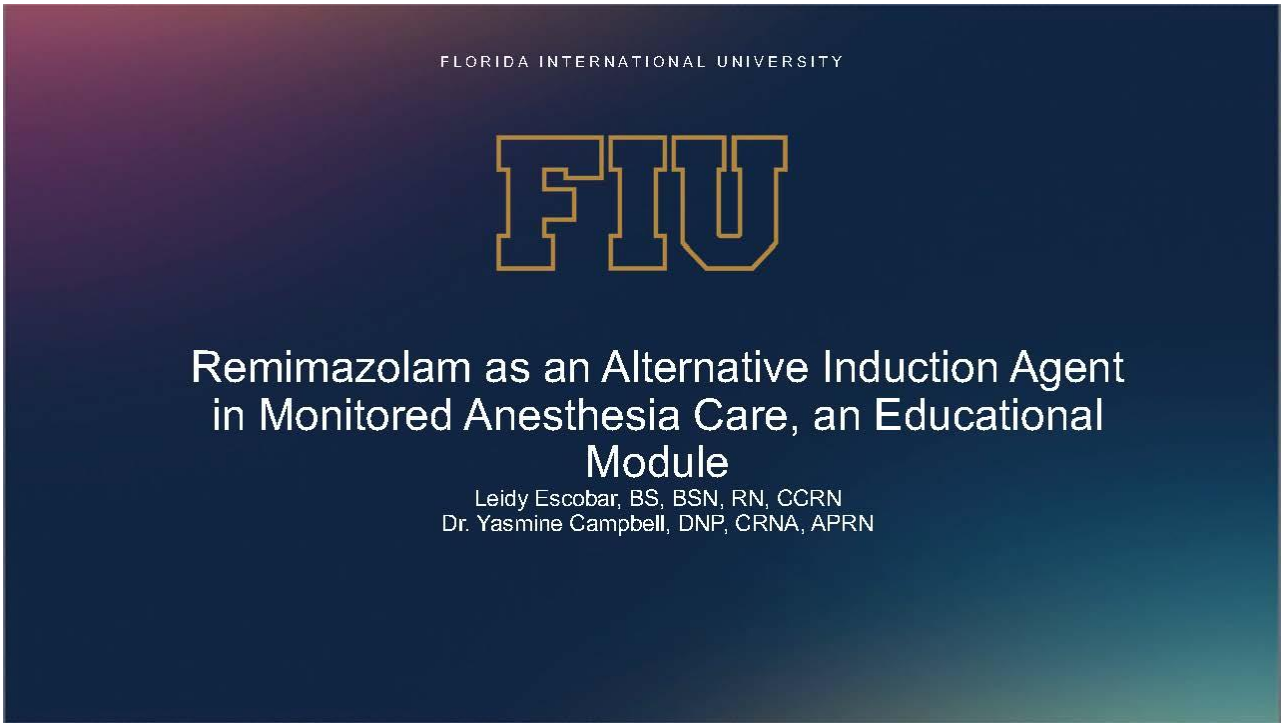
a. Most likely

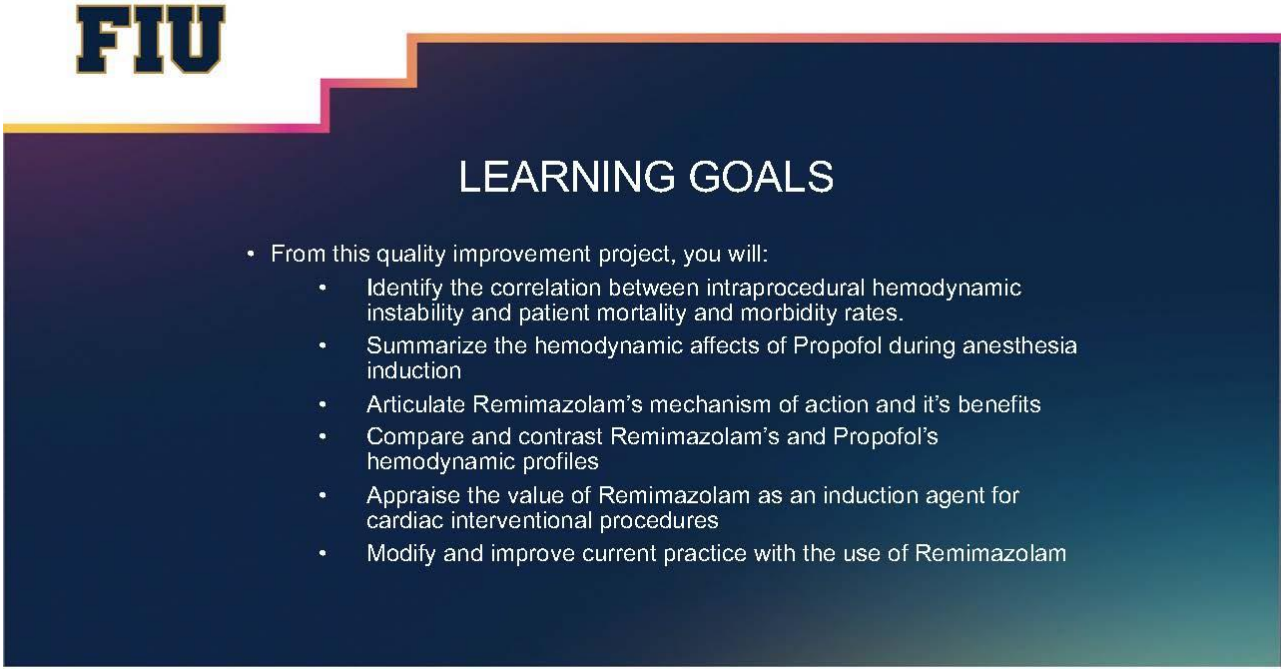
b. Somewhat likely

c. Somewhat unlikely

d. Most unlikely

Appendix F: PowerPoint Presentation for Educational Module





BACKGROUND OF THE PROBLEM

- Postoperative mortality is 1000 times more common than anesthesia related intraoperative mortality
- Myocardial infarction (MI) is the leading cause of postoperative/postprocedural deaths
- Hypotension is strongly associated with periprocedural myocardial infarction, acute kidney injury, and death.
- Approximately a third of all intraprocedural hypotension occurs during the induction of anesthesia.

Scope of the Problem

Mortality and Morbidity

- Sepsis 9%
- Bleeding 14%

MI is the 3rd leading cause of death

- 4% of patients with MI complications die within 1 month
- 90% of MI cases occur within two days of procedure
- 25% of all mortality rates are credited to myocardial ischemia

EDUCATION OF THE PROBLEM

- Hypotension safety thresholds are narrow
- Even brief periods of minor hypotension are linked to complications
- Risk of postprocedural mortality is markedly increased when
  - MAP ≤ 70mmHg for 10 minutes
  - Myocardial injury threshold is MAP ≤ 65mmHg
  - Renal injury threshold is MAP ≤ 75mmH
- Stable hemodynamics is key
- Propofol is the leading intravenous anesthetic for GA and MAC

Propofol

GABA agonist

Quick onset of action

Short half-life

Known to substantially decrease:

Systolic pressure

Diastolic pressure

MAP

CO

SVR

Propofol

Hypotensive states may lead to:	1.5x higher risk of myocardial injury or AKI
	2x higher risk for multiple cardiac complications
Additional adverse effects:	Pain upon administration
	Risk of bacterial contamination

Remimazolam

New FDA approved Benzodiazepine

Direct interaction with GABA receptors and Chloride channels

Inhibits neural activity through an increase in chloride influx

Promising combination of advantages of both Midazolam and Propofol:

Fast onset of action	Short recovery time	Inactive metabolite via esterase activity	Fewer cardio-depressant effects	Reversed via Flumazenil

Remimazolam

Used in multiple settings:

Outpatient procedures
- GI

Minor examinations
- Bronchoscopy
- TEE

General anesthesia
- Non-cardiac elective surgeries
- Cardiac surgery

For various patient populations:

Elderly

Critically ill
- ASA III-IV

Hemodynamically unstable

Liver and kidney insufficiency

Remimazolam vs Propofol

Remimazolam is a safe and effective drug for general anesthesia in ASA I-IV patients

Remimazolam has fewer incidences of adverse reactions compared to Propofol
- No pain during administration

Remimazolam has a superior hemodynamic profile compared to Propofol
- Fewer incidences of hypotension
- Fewer reduction in SBP, MAP, SVR and CO
- Less vasopressor use after induction
- Less need for volume resuscitation after induction

Remimazolam and the Cardiac Patient

Cardiac patients	Remimazolam is an acceptable induction medication for patients with CAD and LVD	During MVR, AVR, or DVR
• Poor cardiovascular reserve function • Low tolerable threshold to the effect of anesthetics on circulatory function	• Remimazolam diminishes hemodynamic fluctuations when compared to Propofol	• Changes in MAP have been found to be considerably more significant with Propofol

Remimazolam for Cardiac Interventional Patients

Cardiac procedures are related to high incidences of postprocedural complications and patient mortality

Hemodynamic stability is critical during cardiac interventional procedures
- Multiple degrees of cardiac dysfunction
- Hemodynamic fluctuations are common

Efficacy of Remimazolam as a sedative hypnotic is non-inferior to Propofol
- Comparable fast onset and recovery
- Less hemodynamic instability
- Propofol has shown to cause hypotension and respiratory depression at even at a lower dose

Electing the appropriate anesthetic induction agent is key
- Reduces organ injuries
- Improves patient prognosis

Take Home Summary

- Remimazolam is safe and efficacious in a multitude of different settings, populations, procedures, and anesthesia techniques
- Same beneficial effects such as hypnosis, sedation, and anti-anxiety as other benzodiazepines
- Similar fast-acting onset and short duration of action as Propofol without being organ dependent for its metabolism
- Non-inferior for the induction of patients for both general and procedural anesthesia with significantly diminished effects on hemodynamics when compared to Propofol
- Reduces detrimental postprocedural effects on multiple organ functions, morbidity, and mortality
- Anesthesia providers now have a safer option for the induction of cardiac interventional patients

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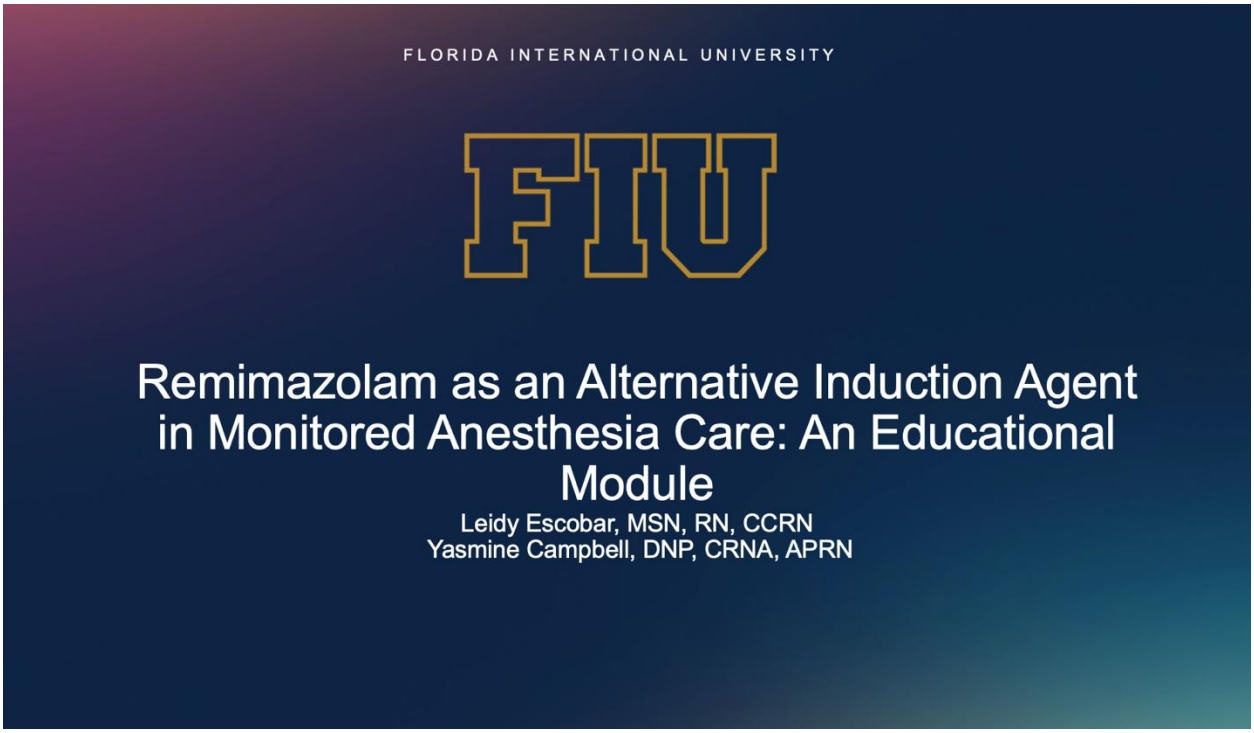
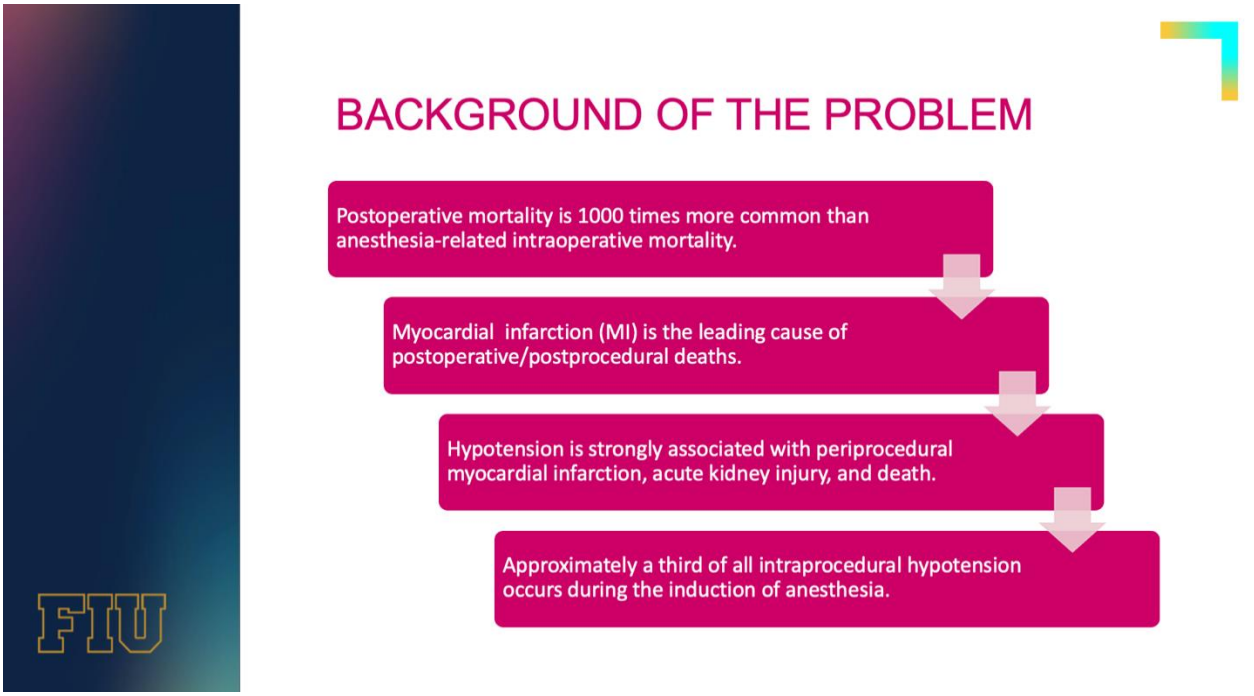
Appendix G: PowerPoint Presentation for Dissemination of Project





Scope of the Problem

Mortality and Morbidity

- Sepsis 9%
- Bleeding 14%

MI is the 3rd leading cause of death

- 4% of patients with MI complications die within 1 month.
- 90% of MI cases occur within 2 days of procedure.
- 25% of all mortality rates are credited to myocardial ischemia.

EDUCATION OF THE PROBLEM

- Hypotension safety thresholds are narrow
- Even brief periods of minor hypotension are linked to complications
- Risk of postprocedural mortality is markedly increased when
  - MAP ≤ 70mmHg for 10 minutes
  - Myocardial injury threshold is MAP ≤ 65mmHg
  - Renal injury threshold is MAP ≤ 75mmH
- Stable hemodynamics is key
- Propofol is the leading intravenous anesthetic for GA and MAC

Consequences of the Problem

- Increased Postoperative Healthcare Resource Utilization
  - Associated with perioperative hypotension
  - 42,800 non-cardiac surgical patients
  - 37.5% experienced perioperative hypotension after induction
  - Extended hospital stay of 4.32 hours/patient
- Additional Losses
  - Patients discharged to care facility
    - Normotensive 18.1%
    - Hypotensive 22.1%
  - Readmission within 30 days of discharge
    - Normotensive 5.0%
    - Hypotensive 6.2%
    - $50.7 billion loss

FLORIDA INTERNATIONAL UNIVERSITY

- Propofol
  - Highly used for induction of monitored anesthesia care
  - Increased postoperative mortality and morbidity
- Remimazolam
  - Superior hemodynamic profile
  - Comparable induction ability to propofol

Purpose

- Educational Quality Improvement Module
  - Directed toward anesthesia providers
  - Education regarding:
    - Hemodynamic effects on morbidity and mortality
    - Hemodynamic profile of both propofol and remimazolam
    - Capability of remimazolam as alternative induction agent for MAC

PICO Question

- In interventional cardiovascular patients receiving monitored anesthesia care, would the use of remimazolam versus propofol decrease hemodynamic instability and reduce the risk of mortality and morbidity?
  - Population (P): Interventional cardiovascular patients
  - Intervention (I): Induction with remimazolam
  - Comparison (C): Induction with propofol
  - Outcomes (O): Effect on hemodynamics; defined by MAP or SBP

Quality Improvement (QI) Methods

Setting and Participants
- Voluntary and anonymous anesthesia providers
- FIU's Department of Anesthesiology Alumni
  - Countrywide anesthesia providers
  - Multi-organizational

Approach and Project Procedures
- Qualtrics
  - Individualized and nontransferable link via email
  - QI Education PowerPoint (PPT) module
  - Pre- and post-assessment survey

QI Methods

- Data Collection/Management
  - Pre- and post-assessment survey responses quantified via Qualtrics
    - Password-protected database
    - Participant identities not associated with data/analysis
- Data Analysis
  - Data comparison via Excel
  - Benchmark
    - 20% or higher from pre- to post-assessment
    - Average of 85% or higher in the post-assessment survey

QI Results

Participant Demographics

Participants (N = 11)	Number (N)	%
Gender		
Male	7	63.64%
Female	4	36.36%
Ethnicity		
Caucasian	5	45.45%
African American	3	27.27%
Hispanic	2	18.18%
Asian	1	9.09%
Other	0	0.00%
Position		
CRNA	11	100%
Level of Education		
MSN	0	0.00%
DNP	11	100%
Years of Experience		
0 – 1	5	45.45%
1-2	5	45.45%
2– 5	0	0.00%
5-10	0	0.00%
Over 10yrs	1	9.09%

Pre- and Post-Survey Responses

Questions	Pretest	Posttest	Change
1. What is the leading cause of postoperative/postprocedural deaths?	N (%)	N (%)	%
Kidney Failure	2 (18.18)	0 (0.00)	18.18
Myocardial Infarction*	8 (72.73)	9 (81.82)	9.09
Sepsis	1 (9.09)	2 (18.18)	9.09
Pulmonary Embolism	0 (0.00)	0 (0.00)	0.00
2. Hypotension is strongly associated with which postprocedural complication?			
Myocardial Infarction	1 (9.09)	0 (0.00)	9.09
Acute Kidney Failure	2 (18.18)	0 (0.00)	18.18
Death	0 (0.00)	1 (9.09)	9.09
All the above*	8 (72.73)	10 (90.91)	18.18
3. Risk of postprocedural mortality is markedly increased when:			
MAP≤60 mmHg for 15 min.	7 (63.64)	1 (9.09)	54.55
MAP≤65 mmHg for 20 min.	4 (36.36)	0 (0.00)	36.36
MAP≤70 mmHg for 15 min.	0 (0.00)	2 (18.18)	18.18
MAP≤70 mmHg for 10 min.*	0 (0.00)	8 (72.73)	72.73
4. Propofol is the medication of choice for the induction of anesthesia because:			
Fast-acting onset and short duration of action*	4 (36.36)	6 (54.55)	18.19
Safest induction medication on the market with the least adverse effects	0 (0.00)	0 (0.00)	0.00
Long duration of action	0 (0.00)	1 (9.09)	9.09
Both A and B	7 (63.64)	4 (36.36)	27.28
5. Propofol has been known to substantially decrease which hemodynamic variable?			
MAP	2 (18.18)	0 (0.00)	0.00
Cardiac Output	0 (0.00)	0 (0.00)	0.00
Systemic Vascular Resistance	2 (18.18)	1 (9.09)	9.09
All the above*	7 (63.64)	10 (90.91)	27.27
6. Remimazolam is a new FDA approved Benzodiazepine with a promising combination of advantages of both:			
Fentanyl and Midazolam	6 (54.55)	0 (0.00)	54.55
Midazolam and Propofol*	4 (36.36)	11 (100.00)	63.64
Propofol and Fentanyl	0 (0.00)	0 (0.00)	0.00
Ketamine and Propofol	1 (9.09)	0 (0.00)	9.09

Pre- and Post-Survey Responses

7. What are some of the benefits of using Remimazolam over Propofol for induction?			
Fewer cardio-depressant effects	1 (9.09)	0 (0.00)	9.09
Inactive metabolite via esterase activity	0 (0.00)	0 (0.00)	0.00
Similar fast-active onset and short duration of action	0 (0.00)	1 (9.09)	9.09
All the above*	10 (90.91)	10 (90.91)	0.00
8. Remimazolam has been proven to be a safe and effective alternative to Propofol during the induction of anesthesia for which procedure?			
Outpatient procedures such as colonoscopies	1 (9.09)	0 (0.00)	9.09
Minor examinations such as bronchoscopies	2 (18.18)	0 (0.00)	18.18
General surgery	0 (0.00)	1 (9.09)	9.09
All the above*	8 (72.73)	10 (90.91)	18.18
9. Propfol has a superior hemodynamic profile compared to Remimazolam?			
True	1 (9.09)	2 (18.18)	9.09
False*	10 (90.91)	9 (81.82)	9.09
10. If available to you, how likely are you to utilize Remimazolam as an alternative to Propofol during the induction of monitored anesthesia care			
Extremely unlikely	1 (9.09)	0 (0.00)	9.09
Somewhat unlikely	1 (9.09)	2 (18.18)	9.09
Neither likely nor unlikely	6 (54.55)	0 (0.00)	54.55
Somewhat likely	2 (18.18)	4 (36.36)	18.18
Extremely likely	1 (9.09)	5 (45.45)	36.36

Discussion

- DNP Benchmark
  - Pre-Assessment Survey
    - Average score 63.6%
  - Post-Assessment Survey
    - Average score 85.5%
  - Acquired Knowledge
    - Increase of 21.9%

Discussion

Limitations

- FIU alumni as sole participants
- Generalizability of findings
- Modest sample size

Online Platform

- Lack of internet access
- Technologically inclined
- Bias sampling

Discussion

Future Implications

- Versatility of remimazolam
  - Induction agent for multiple procedures
  - Adjuvant sedative agent
  - Diverse patient populations
    - Advanced age
    - Obesity
    - ASA III and IV classifications
- Hemodynamic Stability
  - Improvements in postoperative morbidity and mortality rates

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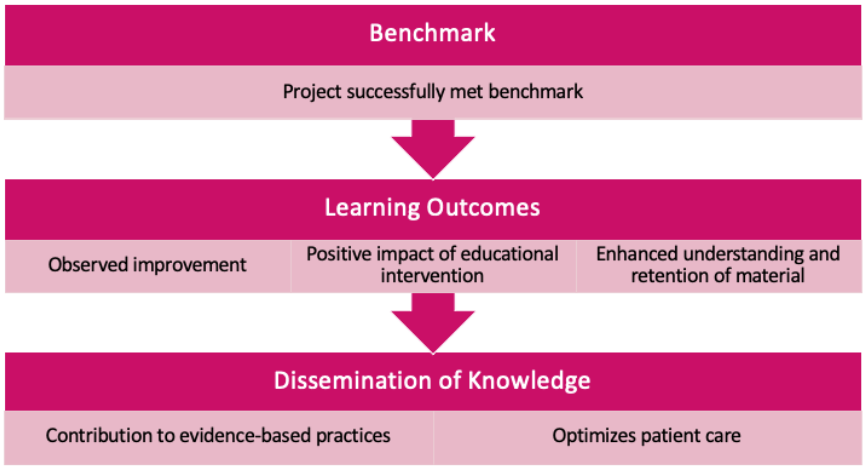
Conclusions



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They say it takes a village, to all those in mine.

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