A Systematic Review Comparing Dexmedetomidine and Fentanyl for Attenuation of the Sympathetic Response to Direct Laryngoscopy

A Major Paper Presented

by

Kerri Secreto

Approved:

Committee Chairperson _____ _____
(Date)

Committee Members _____ _____
(Date)

_____ _____
(Date)

Director of Master's Program _____ _____
(Date)

Dean, School of Nursing _____ _____
(Date)

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Abstract

Sympathetic activation, manifesting as tachycardia and hypertension, is a known occurrence following direct laryngoscopy and endotracheal intubation. Although considered transient and benign in most patients, the marked hemodynamic changes can precipitate perioperative cardiac events in patients with preexisting cardiac risk factors. Perioperative cardiac events are associated with increased morbidity and mortality, prolonged hospitalizations, and increased hospital costs. A multitude of pharmacologic agents have been employed to mitigate the tachycardia and hypertension associated with airway manipulation. Fentanyl is the adjuvant agent most commonly administered to facilitate induction of anesthesia and subsequent airway manipulation. Dexmedetomidine, another adjuvant, has demonstrated effectiveness in suppressing the hemodynamic response to intubation as well as potentially reducing perioperative ischemic events. The purpose of this systematic review was to compare the effectiveness of dexmedetomidine to fentanyl for attenuating the sympathetic response to direct laryngoscopy and endotracheal intubation. Literature and pertinent randomized control trials were searched for inclusion within this review. Four trials were included in this systematic review using the PRISMA checklist. Data was collected from each study and critically appraised using the CASP tool, and a cross analysis was then performed. This systematic review found dexmedetomidine to be superior to fentanyl in attenuating the hemodynamic response to airway manipulation. However, further research is necessary to better determine the effectiveness of these medications on patients with preexisting cardiovascular disease.

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Background/Statement of the Problem

Airway management is essential to safe perioperative care. Direct laryngoscopy is a standard technique in anesthesia practice for securing a patent airway with tracheal intubation by producing a direct line of sight from the operator's eye to the larynx. This technique employs the use of a rigid laryngoscope to displace the structures of the upper airway, exposing the laryngeal inlet to allow visualization of the endotracheal tube (ETT) passage through the vocal cords and into the trachea (Collins, 2014).

While airway management is routine practice, it is not without risks. The manipulation and distraction of the upper airway structures that occurs during anesthetic induction, laryngoscopy, and endotracheal intubation is associated with marked hemodynamic changes and autonomic reflex activity. The sympathetic response elicited by the noxious stimuli results in an increase in circulating catecholamines, which manifests as hypertension, tachycardia, or dysrhythmias occurring within 30 seconds of stimulation and lasting for less than ten minutes (Daabiss et al., 2010). Although the transient hemodynamic changes are of little consequence in otherwise healthy patients, the increased cardiac workload and subsequent increased myocardial oxygen consumption may produce an exaggerated response in those with preexisting cardiovascular disease that can have deleterious consequences (Khanday et al., 2019).

The sympathetic response and resultant adverse effects of direct laryngoscopy and endotracheal intubation in vulnerable populations has been well documented since 1940 when initially observed by Reid and Brace (Reid & Brace, 1940). In a 2013 study, Tosun

et al. reported that 0.6% of patients with ischemic heart disease experienced cardiac complications in the perioperative period, and the perioperative mortality of patients with coronary heart disease undergoing non-cardiac surgery is two to three times that of the general population. Numerous pharmacological agents have been employed in an attempt to attenuate serious cardiac complications caused by such drastic hemodynamic fluctuations. Calcium channel blockers, local anesthetics, beta blockers, and narcotics are among the medications researched, but the varying degree of effectiveness and multitude of adverse side effects found in various pharmacological classes has led to the investigation of alternate solutions.

Fentanyl is a phenylpiperidine-derived synthetic opioid agonist that was first synthesized in 1960 (Flood et al., 2015). As an analgesic that is 75 to 125 times more potent than morphine, fentanyl has been used clinically for the treatment of acute pain as well as to blunt the circulatory response to direct laryngoscopy and tracheal intubation (Flood et al., 2015). Opioids act as agonists at pre and postsynaptic sites in the brain and spinal cord, as well as in the periphery. The principle effect of opioid receptor activation is a decrease of neurotransmission of acetylcholine, dopamine, norepinephrine, and substance P pre-synaptically as well as depression of cholinergic transmission in the central nervous system (Flood et al., 2015). This reduction in sympathetic tone evokes decreases in systemic blood pressure while the increased activity of vagal nerves produces bradycardia and a depressant effect on the sinoatrial node.

Dexmedetomidine is a selective and highly potent alpha-2 adrenoceptor agonist that produces sedative, anxiolytic, sympatholytic, and analgesic effects while causing minimal respiratory depression (Weerink et al., 2017). Dexmedetomidine has been shown

to selectively bind to central pre and postsynaptic alpha-2 adrenergic receptors in the locus coeruleus, inhibiting the release of norepinephrine from synaptic vesicles. (Kumar et al., 2018). This reduction in the sympathetic outflow and subsequent activation of the peripheral sympathetic nervous system causes a reduction in heart rate and blood pressure, and has been found to be beneficial in the setting of myocardial ischemia (Jarineshin et al., 2015). In clinical trials, a single preoperative dose of dexmedetomidine has been shown to attenuate the hemodynamic response to laryngoscopy and endotracheal intubation with minimal side effects (Laha et al., 2013).

Therefore, the purpose of this paper was to conduct a systematic review to compare the effectiveness of dexmedetomidine to fentanyl at attenuating the sympathetic response to direct laryngoscopy and endotracheal intubation.

Literature Review

A comprehensive review of the literature was performed using CINAHL (Cumulative Index to Nursing and Allied Health Literature), MEDLINE/PubMed, and Cochrane Library. An advanced search approach was implemented utilizing key terms "dexmedetomidine" AND "laryngoscopy" AND "fentanyl" AND "sympathetic" AND "hemodynamic". Limitations applied to the search include English language, peer reviewed, and human subjects.

Perioperative cardiac events

The perioperative period, as defined by the Association of perioperative Registered Nurses, begins when a patient is informed of their need for surgery, includes the surgical procedure and recovery, and ends with the resolution of surgical sequalae (2012). More than 200 million adults worldwide undergo noncardiac surgery annually, and of those patients, more than 10 million of those patients experience major cardiac complications within the first 30 days following surgery (Devereaux & Sessler, 2015). According to Devereauz & Sassler, major perioperative cardiac complications account for more than one third of perioperative deaths, result in increased rates of surgical complications, prolonged hospital stays, and increased medical costs (2015). Guidelines by the American Heart Association/American College of Cardiology for preoperative noninvasive risk stratification to evaluate myocardial ischemia in patients with poor functional capacity and an elevated risk for noncardiac surgery are powerful predictors of postoperative cardiovascular events and have decreased the number of cardiac events since their development (Smilowitz & Berger, 2020). Independent risk factors that have been identified for perioperative cardiac morbidity and mortality include high risk surgery, history of ischemic heart disease, congestive heart failure, cerebrovascular

disease, diabetes mellitus, and a serum creatinine level greater than 2mg/dL (Barash et al., 2017). Surgical and anesthetic stimulation are associated with sympathetic nervous system activation, release of inflammatory cytokines such as tumor necrosis factor-a, interleukin-1, interleukin-6, and C-reactive protein, hypercoagulability, hemodynamic compromise, bleeding, and hypothermia which can precipitate cardiac events (Devereaux & Sessler, 2015). Anesthetic technique can be augmented and individualized to each patient to minimize complications and optimize outcomes, however, the hemodynamic changes that accompany direct laryngoscopy and endotracheal intubation have long been recognized as a cardiac stressor, particularly to those with individual cardiac risk factors.

Laryngeal Anatomy

The larynx is a dynamic complex structure composed of nine cartilages held together by intrinsic and extrinsic muscles and ligaments that serves as the entrance to the trachea (Barash et al., 2017). The cartilage, muscles, and ligaments of the larynx function to protect the lower airway from aspiration, provide patency between the hypopharynx and trachea, act as protective reflexes, and provide phonation (Nagelhout & Plaus, 2014). In the adult, the larynx begins at the third or fourth cervical vertebrae and extends to the sixth cervical vertebra. The larynx is subdivided into three regions: the supraglottis, glottis, and subglottis. The supraglottis encompasses the area above the true vocal cords and includes the epiglottis, the false vocal folds, aryepiglottic folds, and arytenoids. The glottis consists of the true vocal folds. The subglottis begins inferior to the glottis and extends to the inferior border of the cricoid cartilage (Nagelhout & Plaus, 2014).

The larynx is innervated by two branches of the vagus nerve, the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN), as well as sympathetic

fibers. The SLN, which branches from the vagus nerve just beyond the jugular foramen at the skull base, and at the level of the hyoid, divides into an internal branch and external branch (Nagelhout & Plaus, 2014). The internal SLN penetrates the thyrohyoid membrane between the greater cornu of the hyoid bone, and provides sensory innervation to the laryngeal cavity superior to the glottis, visceral afferents to the epiglottis, and preganglionic parasympathetic fibers. The external SLN supplies the cricothyroid muscle with visceral efferent and motor innervation(Nagelhout & Plaus, 2014). The RLN provides sensory innervation to the subglottic area and the trachea and motor innervation to all of the muscles of the larynx, except the cricothyroid. Both sides of the epiglottis are densely innervated by both the vagus and glossopharyngeal nerves (Nagelhout & Plaus, 2014). The glottic surface is more sensitive, containing more nerve endings than the lingual surface.

Direct Laryngoscopy and Endotracheal Intubation

Endotracheal intubation is indicated for patients necessitating anesthesia for surgery when controlled ventilation, resuscitation, airway access, patient positioning, and duration of procedure are factors that contribute to the overall anesthetic plan (Hagberg et al., 2018). Direct laryngoscopy is a common procedure in modern anesthesia practice where the objective is to provide visualization of the larynx for subsequent tracheal intubation and airway management in the anesthetized patient. Direct laryngoscopy is accomplished with the use of a laryngoscope when the laryngoscope blade is inserted into the mouth, advanced, and used to displace the upper airway anatomy to expose the laryngeal inlet.

The larynx is the most heavily innervated sensory structure of the body (Hagberg et al., 2018). The mucosa of the upper airway, particularly the supraglottic region of the larynx, contain an abundance of superficial sensory receptors that elicit a transient, yet profound, sympathetic response to noxious airway stimulation (Widdicombe & Lee, 2001). Mechanoreceptors with small diameter myelinated fibers, slowly adapting stretch receptors with large diameter myelinated fibers, and polymodal endings of nonmyelinated nerve fibers are the three major types of sensory nerve fibers in the airway, which are mediated by afferent limbs of the glossopharyngeal and vagus nerves (Perez et al., 2015). Stimulation of sensory receptors within the larynx causes reflex sympathetic activation.

Sympathetic activation

Due to dense sensory innervation and the superficial location of sensory receptors in the supraglottic region and trachea, the abnormal force administered during laryngoscopy to lift the epiglottis and expose the laryngeal inlet stimulates activation of the sympathoadrenal system. The cell bodies of the vagal sensory nerves, which are embedded in the jugular and nodose ganglia, send afferent signals to the nucleus tractus solitarius in the brainstem, initiating widespread autonomic activation through the sympathetic and parasympathetic nervous systems, as well as stimulation of the central nervous system (Hagberg et al., 2018). The autonomic response to noxious airway stimulation, mediated by the cardioaccelerator nerves and sympathetic chain ganglia results in the widespread release of norepinephrine and epinephrine from postsynaptic adrenergic nerve terminals as well as the adrenal medulla (Hagberg et al., 2018). Increased circulating catecholamines stimulate beta-adrenergic receptors within the myocardium, resulting in elevations in heart rate and myocardial contractility, as well as

vascular beta-adrenergic receptors, leading to increased systemic vascular resistance and elevated cardiac afterload (Vermeulen et al., 2018). Direct stimulation of beta-adrenergic nerves also leads to activation of the renin-angiotensin system, furthering the hypertensive response.

Cardiovascular effects of sympathetic activation

Tachycardia and hypertension can lead to ominous complications, like arrythmias or ischemic electrocardiographic changes resulting from increased myocardial oxygen consumption, increasing myocardial resting wall tension, and impaired subendocardial blood flow (Perez et al., 2015). This may aggravate or incite myocardial ischemia in patients with underlying coronary artery disease. In a normal heart, an increase in myocardial oxygen demand causes an increase in coronary artery blood flow and oxygen delivery. The myocardium, because of its limited anaerobic capacity and near maximal oxygen extraction at the cellular level at rest, requires a close match of coronary blood flow relative to its oxygen demand (Vermeulen et al., 2018). Heart rate, and to a lesser extent, myocardial wall tension and contractility, are the primary determinants of oxygen consumption and demand. Tachycardia not only increases myocardial oxygen consumption per minute at a constant wall tension, but the increase in rate results in a reduced diastolic period (Hagberg et al., 2018). The impaired diastolic relaxation subsequently increases resting wall tension, further impairing subendocardial blood flow and further reducing myocardial oxygen supply (Hagberg et al., 2018).

Physiological increases require coronary vasodilation to increase coronary blood flow to maintain oxygen delivery and cardiac function. The increase in coronary blood flow that occurs with augmented myocardial oxygen demands is regulated by alterations

in the diameter and vascular resistance of the coronary arteries (Feliciano & Henning, 1999). Changes in coronary vascular resistance in response to increase in oxygen demand are regulated by endothelial, metabolic, myogenic, and neurohumoral mechanisms. However, in the presence of coronary artery disease, systemic hypertension, and atherosclerosis, the capacity of the coronary vessels to dilate in response to increased myocardial oxygen requirements is significantly reduced (Feliciano & Henning, 1999). Myocardial ischemia results from an imbalance between myocardial oxygen supply and demand.

The noxious stimulation caused from upper airway manipulation elicits an exaggerated cardiovascular response, manifesting as transient tachycardia and hypertension. Reflex changes following intubation led to a 40 to 50% increase in blood pressure and 20% increase in heart rate, on average (Bruder et al., 1992). Russell et al. (1981) concluded from their research that endotracheal intubation is associated with an increase in plasma norepinephrine, a rise in arterial pressure, and an increase in premature ventricular contractions, suggesting an increase in sympathetic activity. In a study conducted by Shribman et al. (1987) it was concluded that the sympathoadrenal response, manifesting as increased arterial blood pressure, tachycardia, and increased serum catecholamine concentrations, to direct laryngoscopy was elicited by tissue tension in the supraglottic region produced by stimulation of vagal and cardiac accelerator fibers. Various strategies, such as minimizing the duration of laryngoscopy, use of a laryngeal mask airway, and a multitude of medications, have been employed to blunt these responses in high risk individuals.

Fentanyl

Fentanyl is a synthetic opioid that has a high affinity for the mu opioid receptor and a low affinity for the delta and kappa opioid receptors, and is used widely in the clinical setting to supplement general anesthesia (Barash et al., 2017). Fentanyl is highly lipid soluble and rapidly crosses the blood brain barrier, which results in a faster onset and an analgesic potency 100 times greater than morphine. According to Barash et al., rapid distribution to vascular organs and other tissues contribute to the drug's short duration of action, further increasing its appeal. In the setting of anesthesia, fentanyl is an attractive option for induction and direct laryngoscopy because single dose administration causes relaxation of pharyngeal, laryngeal and jaw musculature, suppresses the cough reflex, and provides sedation and analgesia (Hagberg et al., 2018). Notably, when administered in doses that prevent a hemodynamic response to intubation, the duration of action of fentanyl is extended such that prolonged postoperative respiratory depression may occur (Hagberg et al., 2018).

Opioid receptor activation results in a decrease in neurotransmission of acetylcholine, dopamine, norepinephrine, and substance P, largely by presynaptic inhibition, although postsynaptic inhibition may occur as well (Flood et al., 2015). Binding of an opioid receptor leads to increased intracellular potassium conductance and hyperpolarization, calcium channel inactivation, or both, triggering an immediate decrease in neurotransmitter release (Flood et al., 2015). Analgesia and sedation are produced with low doses while anesthesia and attenuation of the sympathetic response to stress are elicited with higher doses of fentanyl. Due to its vagomimetic action, variable bradycardia is possible, and due to a reduction in systemic vascular resistance and carotid

sinus baroreceptor reflex, hypotension is a common occurrence (Barash et al., 2017). Other adverse effects associated with fentanyl use include a dose dependent depression of the respiratory centers in the brain, decreased ventilatory response to hypercapnia and hypoxia, delayed gastric emptying, stimulation of the chemoreceptor trigger zone leading to nausea and vomiting, chest wall rigidity, pruritus, and urinary retention.

Fentanyl is frequently used to attenuate the sympathetic response to direct laryngoscopy. In a small randomized study conducted by Dahlgren and Messeter (1981), 5 mcg/kg fentanyl was given as pretreatment for laryngoscopy to a group of eight patients presenting for elective intracranial surgery while normal saline was given to the control group of seven patients. It was found that the group of patients who received the fentanyl pretreatment had a significant reduction in blood pressure and heart rate when compared to the control group. In a randomized control trial of 170 patients, Ko et al. (1998) examined the optimal time of administration of low dose fentanyl to attenuate hemodynamic response to laryngoscopy and intubation. Patients were randomly assigned to groups and received 2mcg/kg fentanyl at 1, 3, 5, or 10 minutes prior to intubation. Ko et al. concluded that fentanyl given 5 minutes prior to intubation effectively attenuated increases in heart rate, mean arterial pressure, systolic blood pressure (SBP) and diastolic blood pressure (DBP) where as doses given at 1 minute and 10 minutes prior to intubation were ineffective at preventing increases in the measured parameters.

Hosalli et al. (2014) conducted a study on 50 ASA I and II adult patients undergoing elective surgery under general anesthesia to determine the optimal dose of fentanyl to effectively abolish the cardiovascular response to laryngoscopy and intubation. ASA class I are those defined as normal, healthy patients, and ASA class II are

defined as patients with mild systemic disease (American Society of Anesthesiologists, 2014). The patients were randomly assigned to receive either 3mcg/kg or 5mcg/kg of fentanyl three minutes prior to intubation, and the heart rate and systolic blood pressure were measured at induction, at intubation, and at 1, 3, and 5 minutes after intubation. The study found that there was no statistically significant difference in the mean heart rate between the 3mcg/kg and 5mcg/kg groups ($p>0.05$). However, mean arterial pressure decreased significantly more in the 5mcg/kg group and remained so until 5 minutes after intubation compared to the 3mcg/kg group, and the rate pressure product was also significantly lower in the 5mcg/kg group at 3- and 5-minutes post intubation. Hosalli et al. (2014) concluded that 5mcg/kg fentanyl dose was more effective at blunting the hemodynamic response to laryngoscopy.

Dexmedetomidine

Dexmedetomidine, an imidazole derivative, is a selective and highly potent alpha-2 adrenoceptor agonist that is commonly utilized in the clinical setting as an adjuvant anesthetic medication (Xu et al., 2014). Clinically, dexmedetomidine produces sedative, anxiolytic, analgesic, and sympatholytic effects while causing minimal respiratory depression (Weerink et al., 2017). Dexmedetomidine has been shown to selectively bind to central pre- and postsynaptic alpha-2 adrenergic receptors in the locus coeruleus (Kumar et al., 2018). Alpha 2 receptors are located peripherally and in the central nervous system and spinal cord. Peripherally, alpha 2 receptors are located on the blood vessel and mediate vasoconstriction as well as in sympathetic terminals where they inhibit norepinephrine release. Centrally, receptors modulate sympathetic outflow and cardiac-vagal activity. Within the spinal cord, alpha 2 receptors modulate pain pathways.

The alpha 2 agonist demonstrates a dose dependent effect, where low doses result in a reduction of sympathetic tone due to decreased norepinephrine release at the neuroeffector junction as well as inhibition of neurotransmission in the sympathetic nerves (Laha et al., 2013). This significant decrease of circulating catecholamines manifests clinically as a modest decrease in heart rate and blood pressure. In clinical trials, a single preoperative dose of dexmedetomidine has been shown to attenuate the hemodynamic response to laryngoscopy and endotracheal intubation with minimal side effects (Laha et al., 2013). In a randomized control study conducted by Laha et al., a single dose of 1mcg/kg dexmedetomidine was administered to a group of 25 patients undergoing major elective surgery and compared to a control group. A significant increase in blood pressure was observed in the control group while the dexmedetomidine group exhibited only a modest increase, suggesting dexmedetomidine attenuated the sympathetic response to direct laryngoscopy.

Due to the ability of dexmedetomidine to attenuate sympathetic outflow, it has been evaluated as an adjunct to potentially reduce cardiovascular complications in the perioperative setting. In a study using an isolated rat heart, Okada et al. (2007) found that dexmedetomidine exhibited an alpha-2 adrenoceptor mediated cardioprotective effect against global ischemia. Dexmedetomidine administration has also been shown to improve circulatory stability and results in a reduction in the intra and postoperative cytokines, leukocytes, and C-reactive protein level in patients presenting for cardiac surgery (Jalonen et al., 1997).

As previously mentioned, the noxious stimulation associated with direct laryngoscopy and endotracheal intubation can stimulate the sympathetic stress response

and result in varying degrees of myocardial injury. Due to the overwhelming evidence citing adverse outcomes following sympathetic response, dexmedetomidine use to attenuate the hemodynamic response related to direct laryngoscopy has been examined. Xu et al. (2014) examined the effects of dexmedetomidine on perioperative myocardial injury by observing peripheral changes in response to intubation and extubation in patients with coronary heart disease undergoing non-cardiac surgery. The randomized control trial examined eighty patients with coronary heart disease undergoing elective hip replacement surgery, and the patients were randomly allocated to receive a loading dose of 1mcg/kg dexmedetomidine followed by a 0.2mcg/kg continuous infusion (dexmedetomidine group) or to receive normal saline (control group). A correlation between dexmedetomidine administration and hemodynamic stability after intubation and extubation was noted. In the study, the patients in the dexmedetomidine group had a lower mean arterial pressure ($P < 0.05$), heart rate ($P < 0.05$), and improvement rate of myocardial ischemia, measured by partial or complete resolution of ST (87.5%) compared to the control group (32.5%; $P < 0.05$). Additionally, serum creatine kinase-MB, cardiac troponin I, glycogen phosphorylase BB, interleukin-6, and tumor necrosis factor-alpha level proteins were measured prior to surgery, at the end of surgery, and at postoperative hour 12 and 24. The enzyme levels increased in both groups at the completion of surgery, yet the dexmedetomidine group exhibited lower serum levels of serum creatine kinase-MB, cardiac troponin I, glycogen phosphorylase BB, and interleukin-6 ($P < 0.05$), suggesting that dexmedetomidine can reduce activation of the cardiac sympathetic system, thus reducing the degree of myocardial injury. There was no

significant difference in tumor necrosis factor-alpha levels between the two groups (P>0.05) (Xu et al., 2014).

Dexmedetomidine and Fentanyl

Noting the effectiveness of both dexmedetomidine and fentanyl in blunting cardiovascular response to noxious stimuli, Aksu et al. (2009) conducted a study to examine which medication was more effective in attenuating airway reflex responses and maintaining hemodynamic stability to tracheal extubation. In this double blinded, randomized control trial, forty ASA I or II patients undergoing elective rhinoplasty with endotracheal intubation were randomly assigned to receive either dexmedetomidine 0.5mcg/kg or fentanyl 1mcg/kg diluted in 100ml isotonic saline intravenously 5 minutes prior to extubation. Heart rate (HR), SBP, DBP, and SpO2 were recorded prior to anesthesia, after drug administration, after skin incision, at the completion of surgery, and 1, 5, and 10 minutes before and after tracheal extubation. Any occurrence of laryngospasm, bronchospasm, or desaturation were noted. The results of the study suggested dexmedetomidine given prior to extubation is associated with less coughing, better quality of extubation, and more attenuation of the cardiovascular response to extubation. The mitigation of coughing in the dexmedetomidine was significantly higher than those in the fentanyl group (85% versus 30%; p=0.001). There was no significant increase in HR from baseline values in the dexmedetomidine group after extubation, whereas HR was significantly increased from baseline at 1, 5, and 10 minutes after extubation in the fentanyl group (p=0.007). HR in the fentanyl group was also found to be significantly higher at 1, 5, and 10 minutes post extubation compared to the dexmedetomidine group at these times (p=0.003). Systolic BP was significantly increased

in the dexmedetomidine group at 1 and 5 minutes after extubation (both, p=0.033) and at 1, 5, and 10 minutes after extubation in the fentanyl group (all, p=0.033). Diastolic BP, compared to baseline values, did not significantly increase in the dexmedetomidine group, but it was significantly increased 1 minutes after extubation in the fentanyl group (p=0.033) and was significantly higher 10 minutes after extubation when compared to the dexmedetomidine group (p=0.047). There were no differences noted in SpO2 between the two groups, and desaturation was not observed in any patients. The groups did not differ significantly with regards to incidence of adverse events.

Framework

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework was used as a guideline to conduct this systematic review. The PRISMA statement is composed of a four-phase diagram (Appendix A), which outlines the flow of information through the various stages of a systematic review, including identification, screening, eligibility, and studies included (Moher et al., 2009). The structure and format provided by PRISMA demonstrates quality of review, ease of assessment, and replication of review method. The PRISMA checklist is an evidence-based set framework composed of a 27-item checklist designed to optimize transparent and complete reporting of systematic reviews and meta-analyses (Moher et al., 2009). The PRISMA checklist (Appendix B) consists of seven sections, including title, abstract, introduction, methods, results, discussions, and findings (Moher et al., 2009). Using the PRISMA checklist, in addition to guidelines for critiquing systematic reviews by Polit and Beck (2017), published research can be critically appraised.

Method

Purpose

The purpose of this study was to compare the effectiveness of dexmedetomidine to fentanyl in attenuating the hemodynamic changes associated with direct laryngoscopy and endotracheal intubation. The primary factors examined were HR in beats per minute, SBP, DBP, and MAP measured in mmHg. Secondary outcomes that were explored include occurrence of adverse side effects, such as bradycardia, hypotension, and cardiac arrythmias. A systematic review of multiple randomized controlled-trials (RCT) was directed to investigate the clinical question. The PRISMA framework was used as a guideline to conduct this systematic review.

Inclusion/Exclusion Criteria

Inclusion criteria for the studies included: (a) randomized controlled-trials, (b) adult patients aged 18 and older (c) elective surgery requiring endotracheal intubation and general anesthesia, (d) ASA class I or II, (e) intervention: intravenous dexmedetomidine, (f) comparison: intravenous fentanyl, (g) outcomes: heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, adverse side effects.

Exclusion criteria for the studies included: (a) patients under the age of 18 years old, (b) non-elective surgery, (c) ASA class other than I or II, (d) patients with cardiovascular disease, chronic obstructive pulmonary disorder, hypertension, or epilepsy, (e) patients with a history of allergy to any of the drugs used during the study, (f) studies that included study drugs other than dexmedetomidine and fentanyl.

Search Strategy

The PRISMA checklist and flow diagram were used to guide the search strategy. A comprehensive review of the literature was performed using CINAHL (Cumulative

Index to Nursing and Allied Health Literature), MEDLINE/PubMed, and Cochrane Library. An advanced search approach was implemented utilizing key terms "dexmedetomidine", "fentanyl " and "laryngoscopy". The time period searched was from 2015 to 2021. Limitations applied to the search include English language, peer reviewed, and human subjects. The resulting records were screened for inclusion and exclusion criteria.

Data Collection and Synthesis

Each article was meticulously screened and pertinent data from each study was organized into tables created to provide organization for the author. The tables provide summarized information of the articles. Information to be summarized and displayed in Table 1 include purpose of the study, setting, sample size and demographics, and design method. Information to be summarized and displayed in Table 2 include induction drugs used, outcomes measured, results, and limitations of the study.

Table 1- *Data Collection Tool 1*

Purpose	Setting	Sample	Design Method

Table 2- *Data Collection Tool 2*

Drugs used for induction of anesthesia	Outcomes Measured	Results	Limitations

Critical Appraisal

Critical appraisal of included studies was performed using the Critical Appraisal Skills Programme, CASP, checklist to establish the trustworthiness, relevance, and results of published papers. The CASP checklist (Appendix C) is an evidence-based 3-section checklist of eleven questions that enables researchers to assess study designs, internal validity, results, and applicability to clinical practice (Critical Appraisal Skills Programme [CASP], 2017). Composed mainly of "yes" or "no" questions, the short checklist helps the reviewer to systematically establish the significance and relevance of research. Following individual study summary and analysis, a cross-study analysis was applied to all included studies.

Cross Analysis

A cross study analysis of the selected randomized controlled trials was conducted after the data had been organized into data collection tables and critically appraised. To best perform the cross study analysis, a table was formulated to identify the author, dosage of each study drug, timing of administration of study drug relative to anesthesia induction, overall attenuation of hemodynamic response to direct laryngoscopy and intubation, and the occurrence of any adverse events (Table 3). Results were then examined to determine similarities and differences between the studies.

Table 3- *Cross Study Analysis*

Author	Dose (mcg/kg)	Timing of study drug administration	Overall attenuation of hemodynamic response to DL	Adverse events

Results

Data Collection

The PRISMA flow diagram was used to guide the search for relevant literature utilized in this systematic review. Multiple databases were used to identify pertinent randomized control trials, and duplicate records were excluded. Databases used were CINAHL, MEDLINE/PubMed, and Cochrane Library. Key words were searched individually and then combined to produce results. The time period searched was from 2015 to 2021. An initial broad search of "dexmedetomidine" yielded 5,107 results through CINAHL, 4,051 through PubMed, and 5,210 through Cochrane Library. The search was then narrowed by the addition of secondary term "fentanyl". Resulting records from CINAHL, PubMed, and Cochrane Library dropped to 453, 717, and 951 respectively. The search was further narrowed by adding the key word "laryngoscopy". CINAHL, PubMed, and Cochrane Library results yielded 53, 19, and 39 respectively. Duplicate articles were removed, and the remaining 50 articles were then screened for inclusion and exclusion criteria and availability of full text. Of the 12 full text articles available, eight were excluded with reason. Four randomized control trials met the inclusion criteria and were chosen for this review (Figure 1).

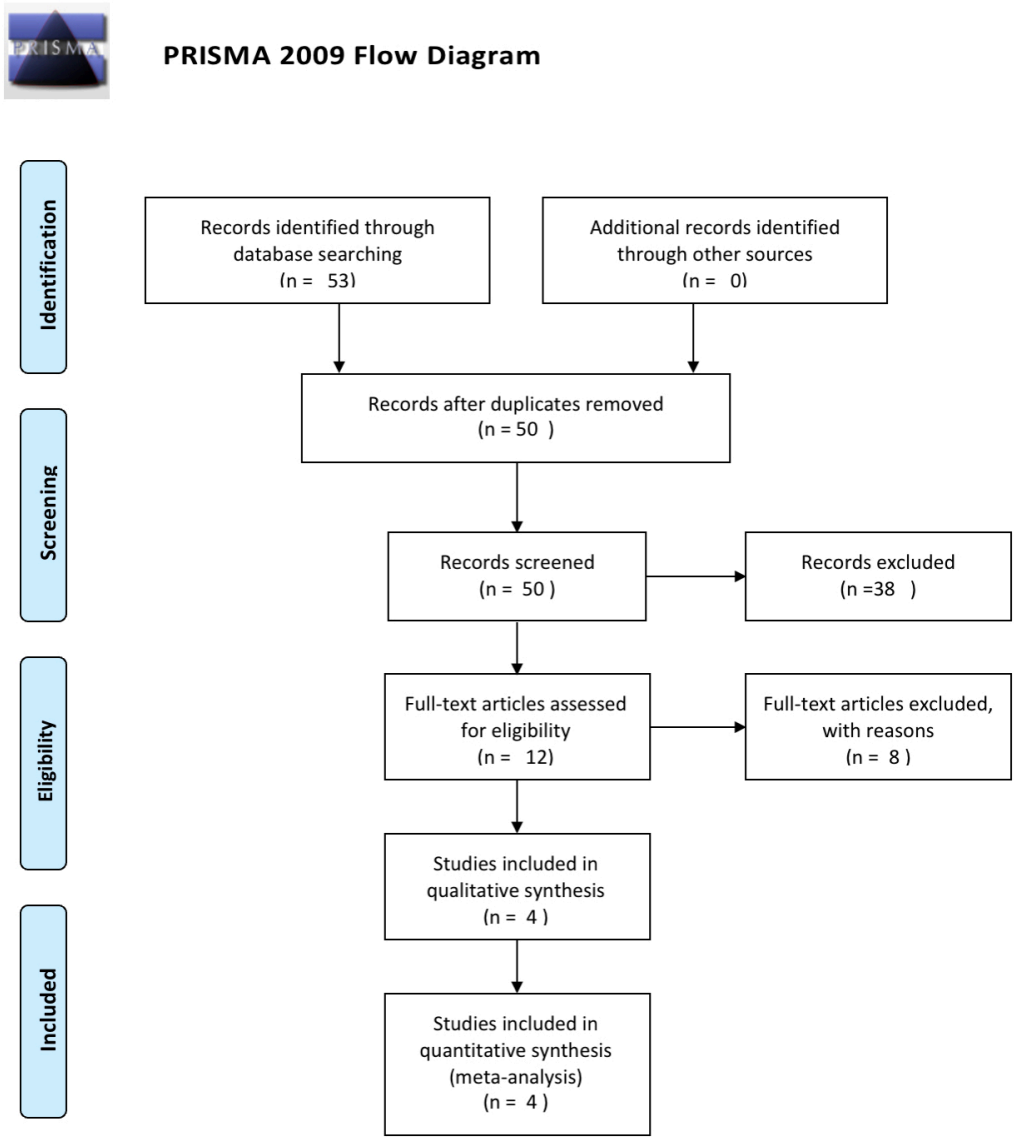

Figure 1. PRISMA Flow Diagram

An RCT by Garg et al. (2020) assessed 100 adult patients undergoing general anesthesia and endotracheal intubation for elective surgical procedures presenting from March to May 2019. The authors calculated that a sample size of 96 participants was

necessary to achieve a power of 80% and a significance level of 0.05. Simple randomization by the chit method randomly divided participants into two groups: Group D, who received dexmedetomidine 1 mcg/kg in 100ml of normal saline infused intravenously ten minutes before direct laryngoscopy and intubation and, Group F, who received fentanyl 2 mcg/kg in 100ml of normal saline infused intravenously ten minutes before direct laryngoscopy and intubation. Heart rate, SBP, DBP, MAP, and SpO2 were monitored continuously from the entry of the patient into the operating room suite and documented at pre-determined intervals from before administration of the study drug until ten minutes following intubation. After completion of the study drug infusion, sedation was measured using the Ramsay sedation scale. Propofol and inhalational isoflurane were used at induction, and propofol dose was determined by loss of eyelash and corneal reflexes. Succinylcholine was the muscle relaxant used for intubation, and direct laryngoscopy was completed within 15 seconds by an experienced anesthesiologist. Comparison showed that the mean heart rate of both groups increased at the time of intubation ($p=0.0465$) and one minute following intubation ($p=0.0462$), however, the increase in heart rate was statistically significant for Group F, showing less attenuation by fentanyl than dexmedetomidine. The mean SBP of both groups was increased at the time of intubation ($p=0.0187$) and one minute after intubation ($p=0.0108$), but the rise was significantly less in the dexmedetomidine group. The rise in MAP was significantly more attenuated by dexmedetomidine at the time of intubation ($p=0.0092$) and one minute after ($p=0.0206$) than fentanyl. There was no statistically significant difference found in SpO2, ETCO2, mean dosage of propofol, or Ramsey sedation scores between the two groups. This study concluded that dexmedetomidine

significantly decreased the sympathetic response of laryngoscopy and intubation as compared to fentanyl. Limitations of the study include no neuromuscular or bispectral index monitoring, no cost analysis, and no measurement of serum catecholamine levels (Appendix D).

Gunalan et al. (2015) conducted a randomized control study comparing the efficacy of bolus administration of intravenous dexmedetomidine with fentanyl in attenuating the cardiovascular stress response accompanying laryngoscopy and intubation. This prospective, double blinded controlled study included sixty ASA I and II adult patients aged 18 to 60, weighing between 50 and 100kg, with Mallampati Grade I and II scores. Participants were excluded based on a history of hypertension, ischemic heart disease, pregnancy, lack of NPO status, emergency surgery, ASA status of III or above, patients with a perceived difficult airway, and those in which the duration of laryngoscopy lasted longer than 25 seconds. Computer generated randomization divided the study population into two groups: Group A received 1 mcg/kg dexmedetomidine in 100ml of normal saline infused over ten minutes and 5ml of normal saline three minutes prior to induction while Group B received 100ml of normal saline infused over ten minutes with fentanyl 2mcg/kg diluted in 5ml of normal saline three minutes prior to induction. All patients were preoxygenated and induced with propofol 2.5mcg/kg over 30 seconds followed by vecuronium 0.1mg/kg as muscle relaxant after confirmation of loss of eyelid reflex. No surgical stimulation was permitted for 10 minutes following intubation to ensure accuracy of results. Heart rate, SBP, and DBP were monitored and recorded prior to induction, after study drug administration, during laryngoscopy and intubation, and at one minute intervals for the succeeding ten minutes. The mean HR in

the dexmedetomidine group decreased after study drug administration and was significantly decreased when compared to the fentanyl for ten minutes following intubation. In the fentanyl group, heart rate increased following laryngoscopy and intubation and remained elevated beyond basal levels for three minutes. The attenuation in SBP, DBP, and MAP was significantly better in the dexmedetomidine group than the fentanyl group after administration of the study drug as well as after intubation. One patient in the dexmedetomidine group exhibited bradycardia that responded to atropine. This study concluded that bolus infusion of dexmedetomidine 1mcg/kg given intravenously over ten minutes provides superior consistent attenuation against the press or response to laryngoscopy and intubation when compared to fentanyl 2mcg/kg. The authors noted a limitation to their study was that they did not measure serum catecholamine levels (Appendix E).

An RCT by Sunil and Santha (2018) explored the adequacy of dexmedetomidine versus fentanyl as a premedication in blunting the hemodynamic changes associated with direct laryngoscopy and endotracheal intubation. Sixty ASA I and II adult patients, aged 18 to 60 years, presenting for elective surgery were randomly divided by computer generated block selection into two groups to receive either dexmedetomidine or fentanyl. Patients in Group D received 1mcg/kg of dexmedetomidine diluted in 10ml of normal saline and administered over ten minutes. Group F received 2mcg/kg of fentanyl diluted in 10ml of normal saline and administered over ten minutes. All patients were then preoxygenated with 100% oxygen for three minutes, medicated with intravenous midazolam 0.03mg/kg, and then induced with intravenous propofol in incremental doses until loss of response to verbal commands was attained. Rocuronium 1.2mg/kg was

administered to achieve neuromuscular blockade, the patient was mask ventilated for 90 seconds, and then a single attempt at direct laryngoscopy was attempted by an experienced anesthesiologist with a standard Macintosh blade. Heart rate, SBP, DBP, MAP, and SpO2 were documented prior to study drug administration, ten minutes after drug administration, and at 1, 5, and 10 minutes following laryngoscopy and intubation. Ramsay sedation scores were measured and recorded following study drug administration and propofol consumption, at the time of induction, was also recorded. Dexmedetomidine was found superior to fentanyl in attenuating an increased heart rate to laryngoscopy after study drug administration ($p<0.001$), one minute after intubation ($p=0.007$), and ten minutes after laryngoscopy ($p<0.001$). There was no statistically significant difference in MAP, SBP, DBP, SpO2, and propofol consumption between the two groups. A higher Ramsey sedation score was observed in Group D (36%) compared to Group F, and three patients in Group D experienced bradycardia, which was treated with atropine. The authors of the study concluded that dexmedetomidine 1mcg/kg as a premedication agent has significant success and is superior to fentanyl 2mcg/kg in suppressing the pressor response to laryngoscopy. Limitations consisted of small sample size and using the fixed single dose of the study drug may limit the evaluation of the dose response effects (Appendix F).

Vaswani et al. (2017) described the hemodynamic changes following administration of dexmedetomidine and fentanyl as premedication drugs to endotracheal intubation in adult patients undergoing laparoscopic surgery. In this RCT, sixty adult patients admitted for different laparoscopic procedures from January 2013 to January 2014 were randomly allocated into two groups using sequentially numbered envelopes.

Sample size required thirty participants in each group to achieve power of 0.9 and type 1 error 0.05. Inclusion criteria included ASA I or II and patients 18 to 60 years old of either gender. Patient criteria for exclusion were pregnancy, lactating, history of acute or chronic renal failure, compromised cardiovascular function, severe deranged liver function, uncontrolled systemic disease, on beta blockers, heart rate less than 55, and emergency procedures. Group D received 0.5mcg/kg of dexmedetomidine over ten minutes prior to induction. Group F received 0.5mcg/kg of fentanyl over ten minutes prior to induction. The patient was preoxygenated with 100% oxygen for three minutes, then glycopyrrolate 0.2mg, ondansetron 4mg, and tramadol 2mg/kg were administered to each patient intravenously. Anesthesia was induced with thiopentone 4 to 5 mg/kg until loss of eyelash reflex was noted. Atracurium 0.75mg/kg was used to achieve neuromuscular blockade. The patient was then mask ventilated for three minutes with 100% oxygen and isoflurane 0.8%, which was followed by laryngoscopy and tracheal intubation. Electrocardiogram tracing (ECG), HR, RR, SBP, DBP, MAP, and SpO2 were recorded continuously and documented at predetermined intervals as followed: prior to infusion of the study drug, ten minutes after infusion of the study drug, after administration of induction medication, after intubation, and five minutes after intubation. Sedation was evaluated after completion of study drug infusion and scored with a modified Ramsay sedation scale. Ramsay sedation scores were significantly higher in Group D than Group F ($p=0.001$). Group F had a statistically significant increase in HR after intubation ($p=0.001$) and 5 minutes after intubation ($p=0.001$) compared to Group D. Group F had a statistically significant rise in SBP after administration of induction medications, immediately after intubation, and also 5 minutes after intubation

(p=0.001) compared to Group D. Group F had a statistically significant rise in MAP after administration of study drug (p=0.002), after administration of induction medications (p=0.001), immediately after intubation (p=0.002), and 5 minutes after intubation (p=0.001) compared to Group D. The authors concluded that dexmedetomidine when compared to fentanyl causes greater attenuation of stress response to tracheal intubation. Limitations noted in the study include the small sample size, no measurement of cardiac output, systemic vascular resistance, or serum catecholamine levels, and that the minimal suppression of hemodynamic response seen in the fentanyl may be attributed to the low dose used (Appendix G).

Critical Appraisal

The four randomized control trials discussed were critically appraised using the CASP checklist.

In the study by Garg et al. (2020), adult patients were randomized into two groups of 50 participants each to compare the effectiveness of dexmedetomidine to fentanyl at attenuating the hemodynamic response to direct laryngoscopy and endotracheal intubation. Eight of the eleven critical analysis questions were answered “yes”. The study did not specify if the anesthesiologists, healthcare workers, or patients were blind to the treatment. Because the induction dose of propofol was determined by loss of eyelash and corneal reflexes and not ideal body weight and the dosing parameters for succinylcholine were not disclosed, it is unclear if groups were treated equally outside from the experimental intervention. Confidence intervals were not reported, so the precision of the treatment effect is unclear (Appendix H).

In the study by Gunalan et al. (2015), all participants were divided into two groups by computer randomization. Most critical appraisal questions were answered "yes" except two. The article states that 60 patients were selected for the study, but those who had Cormack and Lahane score III and above and those in which direct laryngoscopy exceeded 25 seconds were excluded from the study. It is unclear how many participants, if any, were removed from the study. The precision of treatment effect is unclear as no confidence intervals were discussed. The patients, healthcare workers, and anesthesiologists were all blinded to the treatment. All participants were treated equally throughout the study (Appendix I).

In the Sunil and Santha (2018) study, all participants were randomly divided into two groups by computer generated block selection. All critical analysis questions were scored "yes" except one question that asked how precise was the estimate of treatment effect. Because the study did not include confidence intervals, the precision is unclear. Both groups were comparable at the start of the trial. All healthcare workers, anesthesia providers and participants were blinded to the treatment. All participants were treated equally throughout the study (Appendix J).

In the study by Vaswani et al. (2017), a total of 60 participants were randomized and enrolled into one of two groups using sequentially numbered envelopes. All personnel involved with the study were blinded to treatment. Both groups were comparable at the start of the study. All patients were treated and monitored equally throughout the study. All clinically important outcomes were considered. It is unclear how precise the treatment effect was as no confidence interval was discussed (Appendix K).

Cross Analysis

The randomized control trials included in this systematic review were analyzed across studies (Appendix L). The cross analysis compared dosage of administered study drugs, timing of study drug relative to induction, overall hemodynamic attenuation of laryngoscopy and intubation by study drug, and the occurrence of adverse events.

The randomized control trials included in this systematic review investigated the effectiveness of dexmedetomidine compared to fentanyl for attenuating the hemodynamic response to direct laryngoscopy and intubation. While the study drugs administered in each randomized control trial was the same, the dosage administered varied. The studies conducted by Garg et al. (2020), Gunalan et al. (2015), and Sunil & Santha (2018) administered 1mcg/kg of study drug to those in the dexmedetomidine group and 2 mcg/kg of study drug to those in the fentanyl group; Vaswani et al. (2017) administered 0.5mcg/kg of study drug to those in the dexmedetomidine group as well as those in the fentanyl group. As demonstrated in the cross-analysis table (Appendix L), all studies reported better hemodynamic attenuation to laryngoscopy and intubation in the dexmedetomidine group.

Timing of study drug administration relative to direct laryngoscopy and endotracheal intubation was then analyzed across all studies included in this systematic review. Three of the studies administered a bolus dose of the respective study drug over ten minutes prior to anesthetic induction, direct laryngoscopy, and endotracheal intubation. In the study conducted by Gunalan et al. (2015), dexmedetomidine was administered as a bolus dose over ten minutes prior to induction while fentanyl was administered as a bolus dose three minutes prior to induction. Although the timing of

drug administration varied across studies, the results established dexmedetomidine more effectively blunted the sympathetic response to direct laryngoscopy and intubation as compared to fentanyl.

Another aspect of each study that was cross analyzed compared the overall attenuation of hemodynamic response to direct laryngoscopy and endotracheal intubation. Dexmedetomidine, overall, was found superior to fentanyl as premedication in suppressing the cardiovascular response in each randomized control trial, however, there were some observed differences in the effectiveness of each drug across studies. All of the randomized control trials in this systematic review reported decreased mean heart rate, mean arterial pressure, systolic blood pressure, and diastolic blood pressure after study drug administration in patients. In the studies by Garg et al. (2020), Sunil & Santha (2018), and Vaswani et al. (2017), increase in mean heart rate above basal level after intubation was observed in both the dexmedetomidine and fentanyl groups, but the dexmedetomidine groups showed more effective attenuation as the magnitude of increase was significantly higher in the fentanyl groups ($p<0.05$). Garg et al. (2020) and Vaswani et al. (2017) reported that the dexmedetomidine group also demonstrated statistically significant attenuation of heart rate as compared to the fentanyl group five minutes after intubation, whereas Sunil & Santha (2018) showed significant attenuation by dexmedetomidine over fentanyl at ten minutes post intubation. The most significant attenuation of heart rate by dexmedetomidine was observed in the study conducted by Gunalan et al. (2015) where heart rate was statistically significantly decreased ($p=0.001$) from baseline after dexmedetomidine administration, and the heart rate remained statistically significantly attenuated below baseline for up to 10 minutes after intubation.

Dexmedetomidine also showed superior attenuation of mean systolic blood pressure, diastolic blood pressure, and mean arterial pressure as compared to the fentanyl group ($p<0.05$) during intubation in the trials conducted by Garg et al. (2020), Gunalan et al. (2015), and Vaswani et al. (2017). Of note, there was no significant difference between the dexmedetomidine and fentanyl groups in attenuation of mean arterial pressure, systolic blood pressure or diastolic blood pressure observed in the study by Sunil & Santha (2018).

The last aspect compared across studies was the occurrence of adverse events related to study drug administration. One incidence of bradycardia, defined by the studies as heart rate less than 50 beats per minute, was observed in the dexmedetomidine group in the studies by Gunalan et al. (2015) and Vaswani et al. (2017) whereas Sunil & Santha (2018) noted three counts. All reported episodes of bradycardia were responsive to treatment by atropine. Vaswani et al. (2017) observed four incidences of tachycardia, defined as a heart rate 30% greater than baseline, in the fentanyl group, which were successfully treated with propofol boluses. No adverse events were reported in patients of either group by Garg et al. (2020). The results of these randomized control trials imply dexmedetomidine can be used to attenuate the pressor response associated with intubation while also maintaining hemodynamic stability, devoid of major adverse effects.

Summary and Conclusions

Endotracheal intubation is performed extensively in modern anesthesia and is considered the gold standard in protecting the airway in the anesthetized patient. Direct laryngoscopy, although routine practice in the intraoperative setting, entails risk to the patient. The manipulation and distraction of the upper airway structures that occurs to provide adequate exposure of the laryngeal aperture induces transient, yet profound hemodynamic changes and autonomic reflex activity. The sympathetic response provoked by noxious airway stimulation results in a surge of circulating catecholamines, manifesting as tachycardia, hypertension, or dysrhythmias occurring within 30 seconds of laryngoscopy and lasting up to ten minutes (Daabiss et al., 2010). Although these responses are of short duration and little consequence in otherwise healthy individuals, deleterious complications may result in patients with underlying cardiovascular disease or intracranial neuropathology (Hagberg et al., 2018). Prevention or reduction of this sympathoadrenal response is an important consideration in anesthesia practice.

Numerous pharmacologic agents have been employed to ameliorate the response to laryngoscopy. Opioids are a mainstay as adjuvants administered during induction of anesthesia to facilitate airway manipulation. Fentanyl, with its marked potency and rapid onset, suppresses the hemodynamic response to intubation in a dose dependent manner (Hagberg et al., 2018). Intravenous dexmedetomidine, when administered as a bolus dose prior to anesthetic induction, suppresses the cardiovascular response to intubation while minimizing the hypotension commonly observed during the quiescent period between induction and surgical incision (Hagberg et al., 2018). The purpose of this paper was to conduct a systematic review to compare the effectiveness of dexmedetomidine to

fentanyl at attenuating the sympathetic response to direct laryngoscopy and endotracheal intubation.

A literature review was conducted using inclusion and exclusion criteria generated by the author. The databases CINAHL, MEDLINE/PubMed, and Cochrane Library were utilized for the search. The PRISMA checklist and flowchart provided guidance for the search strategy. A total of four randomized control trials were selected for inclusion. Each article was meticulously screened and relevant information was organized into data tables. Information summarized from each article and displayed in the data tables included purpose of the study, setting, sample, design method, drugs used for anesthetic induction, outcomes measured, results, and limitations. Following data collection, a critical appraisal was performed on selected articles. The CASP checklist was used to guide the critical appraisal. Analysis across studies focused on the dosage of each study drug, the timing of study drug administration relative to anesthetic induction, the overall attenuation of hemodynamic response to laryngoscopy and intubation, and the occurrence of adverse events.

All four randomized control trials in this systematic review reported dexmedetomidine was superior to fentanyl in attenuating the hemodynamic response to direct laryngoscopy and intubation. The most significant results were found in the study by Gunalan et al. (2015). These results showed the heart rate in the dexmedetomidine group was significantly decreased when compared to the fentanyl group immediately after study drug administration, and a statistically significant reduction in heart rate was seen for up to ten minutes following intubation in the dexmedetomidine group. Adverse events reported in the dexmedetomidine group across studies was limited to several

occurrences of bradycardia that was responsive to atropine. Adverse events reported in the fentanyl group of one study included tachycardia that was responsive to propofol bolus.

After thorough evaluation of the literature, limitations to this systematic review were identified. The primary limitation to this systematic review was that the study drug dosage and timing of study drug administration relative to induction was not uniform across each control trial. The argument could be made that the study drugs blunt the hemodynamic response in a graded manner, thus dose dependent attenuation of the sympathetic response is not an accurate portrayal of the drug's effectiveness. Then, each of the study drugs examined by the control trials required a specific amount of time to achieve effect-site equilibrium after intravenous bolus administration. The argument could be made that if administration of the study drugs was not timed to coincide with the peak effects of each respective agent, it would be expected that suboptimal attenuation of the hemodynamic response to intubation would occur due to inadequate accumulation of the drug at the effect site (Hagberg et al. 2018). While the results were the same for each trial, a stronger correlation could have been made if the study drug dosage and timing of administration was uniform across all studies. In addition, maximum duration of laryngoscopy time and laryngoscopy blade utilized was not listed across each study. Standardization of both of these factors would further support the findings of this systematic review. Although these limitations existed, the purpose of this systematic review was achieved.

Despite limitations, this systematic review provides evidence that dexmedetomidine is superior to fentanyl at attenuating the sympathetic response associated with laryngoscopy and intubation.

Recommendations and Implications for Advanced Nursing Practice

Sympathetic activation and resultant hemodynamic changes following direct laryngoscopy and endotracheal intubation are an anticipated event to the anesthesia provider. Although usually benign in otherwise healthy individuals, these transient fluctuations can precipitate adverse events in patients with preexisting cardiac disease. In a 2013 study, Tosun et al. reported that 0.6% of patients with ischemic heart disease experienced cardiac complications in the perioperative period, and the perioperative mortality of patients with coronary heart disease undergoing non-cardiac surgery is two to three times that of the general population. Perioperative cardiac complications, despite guidelines aimed to identify those at risk preoperatively, remain a significant source of morbidity and mortality following noncardiac surgery.

There are numerous interventions to decrease the sympathetic response to direct laryngoscopy and intubation. One approach is through the utilization of pharmacologic agents. Fentanyl is the adjuvant most commonly administered to facilitate induction of anesthesia and subsequent airway manipulation, stemming from the historical strategy of utilizing nitrous oxide and narcotics in patients with marginal cardiac reserve (Hagberg et al., 2018). Because fentanyl suppresses the hemodynamic response in a graded manner and does not reach its peak effect until ten minutes after bolus intravenous injection, patients may be subjected to adverse side effects without the desired effect of sympathetic attenuation. Dexmedetomidine is a potent alpha-2 agonist that decreases circulating catecholamines, exhibits an alpha-2 adrenoreceptor mediated cardioprotective effect against global ischemia, and attenuated cardiovascular changes to laryngoscopy (Laha et al., 2013).

This systematic review compared the effectiveness of dexmedetomidine to fentanyl for attenuating the hemodynamic response to direct laryngoscopy and endotracheal intubation. This review provides evidence that dexmedetomidine more effectively attenuates the sympathetic response and maintains hemodynamic stability than fentanyl. Consideration and application of this information could serve to improve patient outcomes. Anesthesia providers need to be educated on the dosage, timing of administration, and circumstances in which dexmedetomidine would be beneficial for use. Additionally, this systematic review has highlighted the need to re-educate anesthesia providers on the appropriate dosing and timing of administration of other pharmacologic agents to maximize their effectiveness. Once education has taken place, this intervention can be incorporated at the clinical level.

Certified Registered Nurse Anesthetists play an integral role in anesthesia care and have the ability to guide patient care and management. After identifying at risk patients, it is the responsibility of the advanced practice nurse to develop and implement individualized anesthetic plans to mitigate the occurrence of adverse cardiac events in the perioperative period. Additionally, it is imperative that evidence based research provides the guidelines by which the advanced practice nurse practices. The ability to understand the quality of evidence presented and then translate the appropriate evidence into practice to guide clinical decisions enables advanced practice nurses to improve patient outcomes.

Although guidelines currently exist to aid in the identification of at risk patients, there has not been a general consensus on which medications prove to be the most beneficial in this patient population. Investigating the effectiveness and the adverse side effects of medication, such as fentanyl and dexmedetomidine, on attenuating the

sympathetic response to laryngoscopy and intubation in healthy populations as well as in those with preexisting disease provides the advanced practice nurse with evidence based research and outcomes. Evidence and outcomes obtained from systematic reviews and published medical literature can then be synthesized to develop clinical practice guidelines to assist practitioners in choosing the appropriate medication intervention for their individual patients and clinical circumstances. This systematic review could aid in future research in formulating clinical practice guidelines for the administration of premedication.

Although dexmedetomidine was found superior to fentanyl when studied in healthy patients, the varying degree of effectiveness across studies warrant further research with more uniform methods to better understand the anticipated outcomes from the medications. Additionally, further research is recommended to determine the effectiveness of these drugs in patients with preexisting cardiac disease. Although more research is required, dexmedetomidine remains an effective treatment for attenuation of the sympathetic response.

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Vaswani, J. P., Debata, D., Vyas, V., & Pattil, S. (2017). Comparative study of the effect of dexmedetomidine vs. fentanyl on haemodynamic response in patients undergoing elective laparoscopic surgery. *Journal of Clinical and Diagnostic Research, 11*(9), 4-8. https://doi.org/10.7860/JCDR/2017/27020.10578

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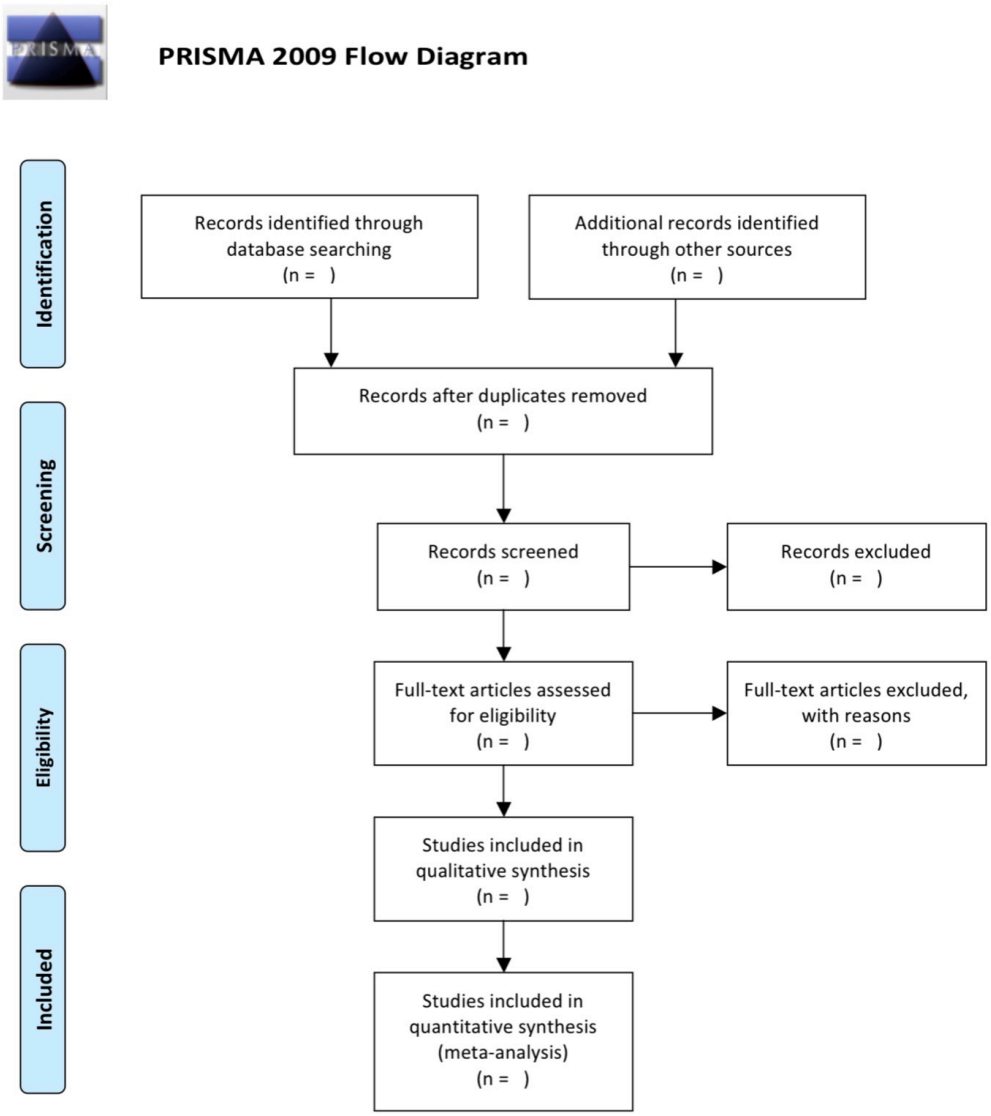
Appendix A



(Mother, et al., 2009)

Appendix B

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

(Moher et al., 2009)

Appendix C

	11 Questions	Yes	Can't tell	no
1	Did the trial address a clearly focused issue?			
2	Was the assignment of patients to treatments randomized?			
3	Were all the patients who entered the trial properly accounted for at its conclusion?			
4	Were patients, health workers and study personnel 'blind' to treatment?			
5	Were the groups similar at the start of the trial?			
6	Aside from the experimental intervention, were the groups treated equally?			
7	How large was the treatment effect?			
8	How precise was the estimate of the treatment effect?			
9	Can the results be applied in your context? (or to the local population?)			
10	Were all clinically important outcomes considered?			
11	Are the benefits worth the harms and costs?			

(CASP, 2018)

Appendix D

Garg, S., Aggarwal, M., Bhat, A., & Rani, A. (2020). Dexmedetomidine versus fentanyl in attenuation of haemodynamic response during laryngoscopy and intubation- a randomized controlled trial. *Journal of Clinical and Diagnostic Research,* 14(4), 1-4. https://doi.org/10.7860/JCDR/2020/43022.13657

Table 1

Purpose	Setting	Sample	Design Method
To compare the effectiveness of dexmedetomidine and fentanyl at attenuating the hemodynamic response to direct laryngoscopy and endotracheal intubation. The secondary aim of the study was to determine if the use of dexmedetomidine or fentanyl resulted in reduction of anesthetic agent use intraoperatively and if that resulted in lower adverse events	-Obtained approval from the college ethical committee of GMC Patiala -Conducted at one hospital	-100 patients, aged 20 to 60 -ASA I or II -Mallampati grade 1 and 2	Participants were randomized into two groups: Group D included those receiving dexmedetomidine 1 mcg/kg in 100ml normal saline given over ten minutes prior to laryngoscopy and intubation Group F included those receiving fentanyl 2mcg/kg in 100ml normal saline given over ten minutes prior to laryngoscopy and intubation -Patients randomized by chit method

Table 2

Drugs used for induction of anesthesia	Outcomes Measures	Results	Limitations
-glycopyrrolate 0.2mg -ondansetron 4mg -ranitidine 50mg -inhalational isoflurane -propofol given in incremental doses until loss of eyelash reflex -succinylcholine (no dosing reported)	-SBP, DPB, MAP, HR, and SpO2 were recorded prior to infusion of study drug, 5 minutes after infusion of study drug, at completion of study drug infusion, at the time of laryngoscopy and intubation, and 1, 3, and 5minutes after laryngoscopy and intubation -Sedation scoring was done per RAMSAY sedation scale after completion of study drug infusion -fall in BP 20% below baseline and pulse rate less than 50 was considered as hypotension and bradycardia respectively	-Mean HR in both groups was highest 10 minutes after intubation, but it was markedly increased in the fentanyl group (p=0.0465). SBP decreased in both groups at study drug infusion completion, but there was no significant difference. There was a rise in SBP in both groups at the time of laryngoscopy, but group D experienced less of an increase than group F (p=0.0187). DBP increased in both groups at laryngoscopy, but was increased less in group D (p=0.0227). MAP also showed less of a rise in group D at the time of laryngoscopy (p=0.0092) and one minute after laryngoscopy (p=0.0206). There was no statistical difference and the values were comparable between group D and group	-Cost effective analysis was not conducted -Blood levels of drug were not measured -Bispectral Index was not used to measure depth of anesthesia -Neuromuscular monitoring was not used

		F in SpO2 and ETCO2 measurements from T0 to T8. The Ramsey sedation score (p=0.5499) and the modified Aldrete score were comparable, with no significant difference found between the groups	

Appendix E

Gunalan, S., Venkatraman, R., Sivarajan, G., & Sunder, P. (2015). Comparative evaluation of bolus administration of dexmedetomidine and fentanyl for stress attenuation during laryngoscopy and endotracheal intubation. *Journal of Clinical and Diagnostic Research, 9*(9), 6-9. https://doi.org/10.7860/JCDR/2015/13827.6431

Table 1

Purpose	Setting	Sample	Design Method
-To compare the efficacy of bolus administration of intravenous dexmedetomidine to intravenous fentanyl in attenuating the cardiovascular stress response to laryngoscopy and endotracheal intubation -To compare any adverse effects associated with the use of dexmedetomidine and fentanyl	-Obtained Institutional Ethical Committee approval -Conducted in a tertiary medical hospital	-60 patients, aged 18 to 60 -ASA I or II -Mallampati 1 or 2 -Weight between 50 to 100kg	-Participants were randomized into two groups by computer generator -Group A: dexmedetomidine 1 mcg/kg in 100ml normal saline given over ten minutes and 5ml normal saline given three minutes prior to laryngoscopy -Group B: 100ml normal saline given over ten minutes and fentanyl 2 mcg/kg in 5ml normal saline given three minutes prior to laryngoscopy

Table 2

Drugs used for induction of anesthesia	Outcomes Measured	Results	Limitations
-alprazolam 0.5mg orally two hours before surgery -500ml lactated ringers -propofol 2.5mg/kg over 30 seconds -vecuronium 0.1mg/kg -mask ventilation with 50% nitrous oxide and 1% sevoflurane for three minutes prior to laryngoscopy	-HR, SBP, and DBP were recorded prior to induction, after administration of the study drug, during laryngoscopy and intubation, and at 1 minute intervals for ten minutes following intubation -Hypotension and bradycardia as adverse effects of the study drugs	-In Group A, the mean HR and BP decreased after administration of dexmedetomidine and did not increase past basal levels in the ten minutes following intubation. -In Group B, the mean HR and BP decreased after administration of fentanyl, but significantly increased after intubation, and returned to baseline within two minutes. -The HRs recorded in Group B remained higher than those recorded in Group A. -One in Group A developed bradycardia	-No measurement of plasma catecholamine levels

Appendix F

Sunil, B. V., & Santha, N. (2018). A prospective randomized controlled trial comparing the effects of dexmedetomidine and fentanyl on attenuation of pressor response during laryngoscopy and intubation. *Anaesthesia, Pain, & Intensive Care, 22*(1), 62-66.

Table 1

Purpose	Setting	Sample	Design Method
-To compare the effectiveness of dexmedetomidine to fentanyl in attenuating the hemodynamic response to direct laryngoscopy and endotracheal intubation	-Obtained Ethics Committee approval -Conforms to the ethical guidelines of the 1975 Declaration of Helsinki -Facility not specified	-60 patients, aged 18 to 60 -ASA I or II	-Participants were randomized into two groups by block randomization technique and concealment was achieved with computer generated block selection -Group D: dexmedetomidine 1 mcg/kg in 10ml normal saline given over ten minutes prior to laryngoscopy -Group F: fentanyl 2 mcg/kg in 1oml normal saline given over ten minutes prior to laryngoscopy

Table 2

Drugs used for induction of anesthesia	Outcomes Measured	Results	Limitations
-alprazolam 0.25mg two hours before surgery -ranitidine 150mg two hours before surgery -preoxygenation for 3 minutes -midazolam 0.03mg/kg -propofol given in incremental doses until loss of response to verbal commands -rocuronium 1.2mg/kg	-HR, SBP, DBP, MAP, and SpO2 were recorded prior to study drug administration, after study drug administration, and 1, 5 and 10 minutes after intubation -Ramsay sedation score after study drug administration -Propofol consumption at time of induction -Incidence of hypotension, hypertension, tachycardia, and bradycardia	-HR response to laryngoscopy and intubation was more in Group F than Group D -Group D had a statistically significant lower HR ten minutes after study drug administration ($p<0.001$), one minute after laryngoscopy and intubation ($p=0.007$), and ten minutes after laryngoscopy and intubation ($p<0.001$) -No statistically significant difference in SBP, DBP, MAP, or SpO2 between Group D and Group F -No statistically significant difference between Group D and Group F in propofol consumption -A significantly higher Ramsey sedation score was observed in Group D than Group F	-Small sample size -Not evaluating the hemodynamic effects of the study drugs until the postoperative period -Studying the fixed single dose of the study drug limited the evaluation of the dose-response effects

		(p=0.016) -Bradycardia observed in three participants in Group D	

Appendix G

Vaswani, J. P., Debata, D., Vyas, V., & Pattil, S. (2017). Comparative study of the effect of dexmedetomidine vs. fentanyl on haemodynamic response in patients undergoing elective laparoscopic surgery. *Journal of Clinical and Diagnostic Research, 11*(9), 4-8. https://doi.org/10.7860/JCDR/2017/27020.10578

Table 1

Purpose	Setting	Sample	Design Method
-To compare the effect of dexmedetomidine versus fentanyl on hemodynamic response to tracheal intubation, following pneumoperitoneum, and intraoperative period in patients undergoing laparoscopic surgery	-Institutional Ethics Committee approval -Conducted at one hospital	-60 patients, aged 18 to 60 -ASA I or II	-Participants were randomized into two groups using sequentially numbered envelopes -Group D: intravenous dexmedetomidine 0.5 mcg/kg in 50ml normal saline given over ten minutes prior to induction -Group F: intravenous fentanyl 0.5 mcg/kg in 50ml normal saline given over ten minutes prior to induction

Table 2

Drugs used for induction of anesthesia	Outcomes Measured	Results	Limitations
-Preoxygenation for three minutes -Glycopyrrolate 0.2mg -Ondansetron 4mg -Tramadol 2mg/kg -Thiopentone 4-5mg/kg until loss of eye lash reflex -Atracurium 0.75mg/kg -Mask ventilation with 100% oxygen and isoflurane 0.8%	-ECG, HR, RR, SBP, DBP, MAP, and SpO2 were recorded prior to administration of study drug, ten minutes after administration of study drug, after administration of induction medications, immediately after intubation, 5 minutes after intubation, immediately, 5, 10, 15, 30, 45, and 60 minutes after pneumoperitoneum, and 5 minutes after release of pneumoperitoneum. -Ramsay sedation score after administration of study drug -Incidence of bradycardia, tachycardia, hypotension, hypertension, nausea, vomiting, and respiratory depression following administration of study drug	-Ramsay sedation scores were significantly higher in Group D than Group F (p=0.001) -Group F had a statistically significant increase in HR after intubation (p=0.001) and 5 minutes after intubation (p=0.001) compared to Group D -Group F had a statistically significant rise in SBP after administration of induction medications, immediately after intubation, and 5 minutes after intubation (p=0.001) compared to Group D. -Group F had a statistically significant rise in MAP after administration of study drug (p=0.002), after administration of induction medications (p=0.001),	-No measurement of cardiac output. Systemic vascular resistance, or serum catecholamine levels -The minimal suppression of hemodynamic response observed in Group F may be due to the low dose used

		immediately after intubation (p=0.002), and 5 minutes after intubation (p=0.001) compared to Group D	

Appendix H

Garg, S., Aggarwal, M., Bhat, A., & Rani, A. (2020). Dexmedetomidine versus fentanyl in attenuation of haemodynamic response during laryngoscopy and intubation- a randomized controlled trial. *Journal of Clinical and Diagnostic Research,* 14(4), 1-4. https://doi.org/10.7860/JCDR/2020/43022.13657

		Yes	Can't Tell	No
1	**Did the trial address a clearly focused issue?** The aim of the study was to compare the effects dexmedetomidine to fentanyl on the hemodynamic response to endotracheal intubation and on anesthetic requirements.	**X**		
2	**Was the assignment of patients to treatments randomized?** Patients were randomized into two groups using chit method.	**X**		
3	**Were all the patients who entered the trial properly accounted for at its conclusion?** All 100 patients who participated finished the study.	**X**		
4	**Were patients, health workers and study personnel 'blind' to treatment?** The study does not specify if the providing anesthesiologists or other healthcare workers are blind to the study.		**X**	
5	**Were the groups similar at the start of the trial?** Both groups were comparable and there was no statistically significant difference with regard to age (p=0.9973), sex (p=0.6484), ASA grade (p=0.8414), body weight (p=0.7269), and duration of surgery (p=0.9355).	**X**		
6	**Aside from the experimental intervention, were the groups treated equally?** Each patient was kept NPO for six hours preoperatively and received 0.5mg clonazepam at 6am the day of surgery. Two 18 gauge IV lines were started and a 500ml bolus of lactated ringers was infused. Pre-induction medications included glycopyrrolate 0.2mg, ondansetron 4mg, and ranitidine 50mg. Propofol dose was determined by "loss of eyelash and corneal reflex", not weight based dosage. Succinylcholine was the muscle relaxant used, but no dosage was listed.		**X**	
7	**Were the effects of the intervention reported comprehensively?** Comparison showed that the mean heart rate of both groups increased at the time of intubation (p=0.0465) and one minute following intubation (p=0.0462), however, the increase in heart rate was statistically	**X**		

	significant for Group F, showing less attenuation by fentanyl than dexmedetomidine. The mean SBP of both groups was increased at the time of intubation (p=0.0187) and one minute after intubation (p=0.0108), but the rise was significantly less in the dexmedetomidine group. The rise in MAP was significantly more attenuated by dexmedetomidine at the time of intubation (p=0.0092) and one minute after (p=0.0206) than fentanyl. There was no statistically significant difference found in SpO2, ETCO2, mean dosage of propofol, or Ramsey sedation scores between the two groups.			
8	**How precise was the estimate of the treatment effect?** Continuous variables were analyzed with unpaired t-test and Mann Whitney U test. Categorical variables were analyzed with the chi-square test. P<0.05 was considered statistically significant where as p<0.001 was considered highly significant. No confidence intervals were reported		**X**	
9	**Can the results be applied in your context? (Or to the local population?)** Findings were appropriate for this systematic review	**X**		
10	**Were all clinically important outcomes considered?** HR, SPB, DBP, MAP, and SpO2 were measured prior to study drug administration, during study drug administration, after study drug administration, at the time of laryngoscopy and intubation, and 1, 3, 5, and 10 minutes after laryngoscopy and intubation.	**X**		
11	**Are the benefits worth the harms and costs?** No patient in this study had adverse effects such as bradycardia, defined by the study as HR <50bpm, hypotension, defined by the study as SBP <90mmHg, DBP <60mmHg, or MAP <50mmHg, or cardiac arrhythmias	**X**		

Appendix I

Gunalan, S., Venkatraman, R., Sivarajan, G., & Sunder, P. (2015). Comparative evaluation of bolus administration of dexmedetomidine and fentanyl for stress attenuation during laryngoscopy and endotracheal intubation. *Journal of Clinical and Diagnostic Research, 9*(9), 6-9. https://doi.org/10.7860/JCDR/2015/13827.6431

		Yes	Can't Tell	No
1	**Did the trial address a clearly focused issue?** The purpose of the study was to compare the efficacy of a bolus dose of dexmedetomidine and fentanyl in attenuating hemodynamic stress response following laryngoscopy and intubation.	**X**		
2	**Was the assignment of patients to treatments randomized?** Patients were allocated into two groups by computer generated randomization	**X**		
3	**Were all the patients who entered the trial properly accounted for at its conclusion?** The article stated that 60 participants were selected for the study, but patients who had Cormack Lahane score III and above and those in which duration of laryngoscopy exceeded 25 seconds were removed from the study. The article does not clearly indicate how many participants, if any at all, were removed from the study.		**X**	
4	**Were patients, health workers and study personnel 'blind' to treatment?** This was a double blinded control study. Medications were prepared by a third party, and the anesthesia providers monitoring the patients as well as the anesthesia providers performing the laryngoscopy and intubation were blinded to the groups.	**X**		
5	**Were the groups similar at the start of the trial?** The demographics data between groups was comparable. Mean age, male to female ratio, and weight for Group A was 32.47±10.93, 18/12, and 58.63±13.4, respectively. Mean age, male to female ratio, and weight for Group B was 31.27 ±10.43, 15/15, and 60.40±12.95, respectively.	**X**		
6	**Aside from the experimental intervention, were the groups treated equally?** All patients received the same IV medications based on body weight and were monitored equally.	**X**		
7	**Were the effects of the intervention reported**	**X**		

	comprehensively? HR was significantly decreased in the dexmedetomidine group compared to fentanyl immediately after study drug administration until 10 minutes following intubation, denoted by p-value less than 0.05. Attenuation in SPB, DBP, and MAP was also significantly better in the dexmedetomidine group than the fentanyl group ($p<0.05$). HR was significantly decreased in the dexmedetomidine group compared to the fentanyl group immediately after study drug administration until 4 minutes following intubation ($p=0.001$).			
8	**How precise was the estimate of the treatment effect?** The statistical methods used in this study were chi square test and students unpaired "t" test. A $p<0.05$ was considered statistically significant. No confidence intervals were discussed in the study.		**X**	
9	**Can the results be applied in your context? (Or to the local population?)** Findings were appropriate for this systematic review.	**X**		
10	**Were all clinically important outcomes considered?** HR, SBP, and DBP were recorded prior to study drug administration, after administration of the study drug, during laryngoscopy and intubation, and at 1 minute intervals for 10 minutes following intubation	**X**		
11	**Are the benefits worth the harms and costs?** One patient in the dexmedetomidine group experience bradycardia, which was effectively treated with atropine.	**X**		

Appendix J

Sunil, B. V., & Santha, N. (2018). A prospective randomized controlled trial comparing the effects of dexmedetomidine and fentanyl on attenuation of pressor response during laryngoscopy and intubation. *Anaesthesia, Pain, & Intensive Care, 22*(1), 62-66.

		Yes	Can't Tell	No
1	**Did the trial address a clearly focused issue?** The purpose of the study was to compare the hemodynamic effects of a single pre-induction dose of dexmedetomidine and fentanyl on laryngoscopy and intubation.	**X**		
2	**Was the assignment of patients to treatments randomized?** Randomization was done by block randomization technique, and concealment was achieved with computer generated block selection.	**X**		
3	**Were all the patients who entered the trial properly accounted for at its conclusion?** All 60 patients completed the study.	**X**		
4	**Were patients, health workers and study personnel 'blind' to treatment?** Medications were prepared by an anesthesiologist not involved in the study. Intraoperative and postoperative assessments were performed by an anesthesiologist blinded to the patient allocations and study groups.	**X**		
5	**Were the groups similar at the start of the trial?** The sample consisted of patients aged 18 to 60 who were all ASA class I or II undergoing elective procedures requiring endotracheal intubation. Patients with a history of allergy to any study drug, history of cardiac disease, hypertension, thyroid dysfunction, uncontrolled diabetes mellitus, liver or renal disease, patients receiving alpha agonists or beta blockers, pregnancy or lactating women, obesity, addiction, psychological disease, or predicted difficult intubation were excluded from the study. Both groups were comparable with regard to age and gender distribution.	**X**		
6	**Aside from the experimental intervention, were the groups treated equally?** Propofol for induction was given in incremental doses until loss of response to verbal command was noted. All other medications were dosed based on weight and monitoring was comparable.	**X**		

7	**Were the effects of the intervention reported comprehensively?** Dexmedetomidine was found superior to fentanyl in attenuating an increase in heart rate to laryngoscopy after study drug administration ($p<0.001$), one minute after intubation ($p=0.007$), and ten minutes after laryngoscopy ($p<0.001$). There was no statistically significant difference in MAP, SBP, DBP, SpO2, and propofol consumption between the two groups. A higher Ramsey sedation score was observed in Group D (36%) compared to Group F.	**X**		
8	**How precise was the estimate of the treatment effect?** The statistical methods used in this study were chi square test and students unpaired "t" test. A $p<0.05$ was considered statistically significant. Data was given as mean (SD) with a corresponding p value. No confidence intervals were reported.		**X**	
9	**Can the results be applied in your context? (Or to the local population?)** Findings were appropriate for this systematic review.	**X**		
10	**Were all clinically important outcomes considered?** Heart Rate, SBP, DBP, MAP, and SpO2 were documented prior to study drug administration, ten minutes after study drug administration, and at 1, 5, and 10 minutes following laryngoscopy and intubation. Ramsay sedation scores were measured and recorded following study drug administration and propofol consumption, at the time of induction, was also recorded	**X**		
11	**Are the benefits worth the harms and costs?** Bradycardia, defined by the study as HR <50 beats per minute, was observed in three patients in the dexmedetomidine group, and was treated to effect with atropine 0.6mg.	**X**		

Appendix K

Vaswani, J. P., Debata, D., Vyas, V., & Pattil, S. (2017). Comparative study of the effect of dexmedetomidine vs. fentanyl on haemodynamic response in patients undergoing elective laparoscopic surgery. *Journal of Clinical and Diagnostic Research, 11*(9), 4-8. https://doi.org/10.7860/JCDR/2017/27020.10578

		Yes	Can't Tell	No
1	**Did the trial address a clearly focused issue?** The aim of the study was to compare the effect of dexmedetomidine versus fentanyl on hemodynamic response to tracheal intubation, following pneumoperitoneum and intraoperative period in patients undergoing laparoscopic surgery.	**X**		
2	**Was the assignment of patients to treatments randomized?** 60 patients were randomly allocated into two groups using sequentially numbered envelopes.	**X**		
3	**Were all the patients who entered the trial properly accounted for at its conclusion?** All 60 patients completed the study.	**X**		
4	**Were patients, health workers and study personnel 'blind' to treatment?** This was a prospective, randomized, double blinded study.	**X**		
5	**Were the groups similar at the start of the trial?** Mean age of Group D was 37.9±13.168 and Group F was 34.7±11.47 (p=0.748); male to female ratio in Group D was 10:20 and Group F was 11:19 (p=0.748); mean weight in kg in Group D was 55.93±10.793 and Group F was 54.13±10.957 (p=0.124); ASA status I/II ratio in Group D was 24/6 and 25/5 in Group F (p=0.739)	**X**		
6	**Aside from the experimental intervention, were the groups treated equally?** All patients received the same IV medications based on body weight and were monitored equally.	**X**		
7	**Were the effects of the intervention reported comprehensively?** Ramsay sedation scores were significantly higher in Group D than Group F (p=0.001). Group F had a statistically significant increase in HR after intubation (p=0.001) and 5 minutes after intubation (p=0.001) compared to Group D. Group F had a statistically significant rise in SBP after administration of induction medications, immediately after intubation, and 5 minutes after intubation (p=0.001) compared to Group D. Group F	**X**		

	had a statistically significant rise in MAP after administration of study drug (p=0.002), after administration of induction medications (p=0.001), immediately after intubation (p=0.002), and 5 minutes after intubation (p=0.001) compared to Group D.			
8	**How precise was the estimate of the treatment effect?** Sample size of 30 per group was determined based on previous study results on outcome, with power of 0.9 and type 1 error 0.05. The results were expressed as number of occurrences percentage, and mean ±SD. Demographic characteristics, preoperative vital signs were compared with Chi-square test. Repeated measures of analysis of variance was used to compare continuous variables. A p-value of <0.05 was considered statistically significant. No confidence interval was discussed.		**X**	
9	**Can the results be applied in your context? (Or to the local population?)** This study is appropriate for this systematic review.	**X**		
10	**Were all clinically important outcomes considered?** ECG, Heart rate, RR, SBP, DBP, MAP, and SpO2 were recorded continuously and documented at predetermined intervals as followed: prior to infusion of the study drug, 10 minutes after infusion of the study drug, after administration of induction medication, after intubation, and 5 minutes after intubation. Sedation was evaluated after completion of study drug infusion and scored with a modified Ramsay sedation scale.	**X**		
11	**Are the benefits worth the harms and costs?** Tachycardia, defined by the study as HR >30% of baseline value, was observed in four patients in the fentanyl group during intubation and was treated with 20mg intravenous propofol. Bradycardia, defined by the study as HR<55 beats per minute, was observed in one patient in the dexmedetomidine group during intubation and was treated with 0.2mg intravenous glycopyrrolate.	**X**		

Appendix L

Author	Dose (mcg/kg)	Timing of study drug administration	Overall attenuation of hemodynamic response to DL	Adverse events
Garg et al., 2020	Dex: 1 Fentanyl: 2	Study drugs were infused over 10 minutes prior to induction	Dexmedetomidine better attenuated the sympathetic response of DL and intubation as compared to fentanyl	No adverse events occurred in either group
Gunalan et al., 2015	Dex: 1 Fentanyl: 2	Dexmedetomidine was administered over 10 minute prior to induction; fentanyl was administered over 3 minute prior to induction	Dexmedetomidine better attenuated the sympathetic response of DL and intubation as compared to fentanyl	One patient in the dexmedetomidine group developed bradycardia
Sunil & Santha, 2018	Dex: 1 Fentanyl: 2	Study drugs were infused over 10 minutes prior to induction	Dexmedetomidine better attenuated the sympathetic response of DL and intubation as compared to fentanyl	Three patients in the dexmedetomidine group developed bradycardia
Vaswani et al., 2017	Dex: 0.5 Fentanyl: 0.5	Study drugs were infused over 10 minutes prior to induction	Dexmedetomidine better attenuated the sympathetic response of DL and intubation as compared to fentanyl	Bradycardia was observed in one patient in the dexmedetomidine group. Tachycardia was observed in four patients in the fentanyl group