

# Attenuation of Hemodynamic Response to Laryngoscopy and Endotracheal Intubation with Pre Induction IV Fentanyl Versus Combination of IV Fentanyl and Sub Lingual Nitroglycerin Spray

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## Abstract

**Introduction:** Endotracheal intubation is one of the most invasive stimuli in anesthesia and it's often accompanied by a hemodynamic pressor response. The purpose of this study was to investigate the efficacy of a single pre-induction 2 µg/kg bolus injection of fentanyl followed by two puffs of nitroglycerin sub lingual spray (400 µg /spray) with a thiopentone/suxamethonium sequence in the attenuation of the hemodynamic response to endotracheal intubation in normotensive patients. **Material and methods:** The study consisted of 80 randomly selected ASA physical status I/II male/female adults who were aged between 18 through 60 years and scheduled for elective surgery. Group I received a single 2 µg/kg IV bolus of fentanyl diluted to 5 ml with normal saline 5 min prior to laryngoscopy followed by two puffs of nitroglycerin sub lingual spray (400 µg/spray) 2 minutes prior to intubation (n=40). Group II received a single 2 µg/kg IV bolus of fentanyl diluted to 5 ml with normal saline 5 min prior to laryngoscopy (n=40). Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product were compared to basal values at pre-induction, induction, intubation and post-intubation as well as at time increments of 1, 3, 5, 7 and 10 min. **Results:** Fentanyl combined with nitroglycerin did not attenuate hemodynamic pressor responses more than fentanyl alone. Increases of HR (7.9%), DBP (4.0%), MAP (3.6%) and RPP (6.0%) along with attenuation of SBP (2.7%) were observed in the fentanyl-nitroglycerin group as compared to the equivalent control measured values. **Conclusions:** A single pre-induction bolus injection of fentanyl followed by two puffs of nitroglycerin sub lingual spray in a thiopentone/suxamethonium anesthetic sequence neither successfully attenuates nor successfully suppresses the hemodynamic pressor response more effectively than fentanyl alone in normotensive patients resulting from endotracheal intubation.

**Key words:** fentanyl, nitroglycerin, endotracheal intubation, hemodynamic response, attenuation.

## 1. INTRODUCTION

Laryngoscopy and intubation are not only common and necessary medical procedures, but also are extremely invasive to the patient with the potential to cause dynamic, possibly dangerous hemodynamic pressor response (1, 2, 3). A typical pressor response can include a 40-50% increase in blood pressure, a 20% increase in heart rate, and an elevation of both epinephrine and norepinephrine levels (4). These effects usually occur within thirty seconds of intubation and last less than ten minutes [5], thus they are generally tolerated well by overall healthy patients. However, these same effects can be lethal to patients with pre-existing conditions such as hypertension, increased intracranial pressure, those who have recently suffered heart

attacks or those who have other conditions that confer increased sensitivity to sudden and severe heart rate or blood pressure changes (1, 2, 3, 6, 7, 8). Therefore, many drugs are often used in combination with the primary anesthetic in an attempt to decrease the hemodynamic pressor response associated with intubation while limiting patient risk. One drug commonly used in conjunction with a primary anesthetic is Fentanyl because it is cost-effective and brings many other advantages (8). As a member of the opioid family, Fentanyl is a µ-opioid receptor agonist that is characterized by high potency, rapid onset, and short duration of action (9, 10) and produces no histamine release—thus avoiding the negative cardiovascular effects caused by such a response (11). Furthermore,

combining fentanyl with anesthetic agents is known to reduce the amount of anesthetic necessary to induce unconsciousness (12). In cases where premedication with fentanyl is inadequate, nitroglycerin (NTG) is another option that studies have shown can be used to prevent stress-induced ischemia and to relieve the constriction of coronary arteries (13). However, administration of NTG alone during pre-intubation may not be sufficient to completely mediate hemodynamic response due to its tendency to produce tachycardia (5). Currently, no single drug has been able to completely inhibit the stress response to laryngoscopy and intubation. However, combination drug therapy may be able to better blunt this response. To date, a few studies have evaluated the combination of fentanyl and NTG with respect to their affect on hemodynamic response (14, 15). However, administration of NTG alone during pre-intubation may not be sufficient to completely mediate hemodynamic response due to the tendency of NTG to produce tachycardia<sup>5</sup>. Despite the efficacy demonstrated in previous studies, in-depth analysis and ideal dose combination of fentanyl and NTG required to suppress the hemodynamic response to endotracheal intubation has not yet been determined. Therefore, the purpose of this study is to investigate whether a single 2 µg/kg bolus pre-induction injection of fentanyl administered 5 minutes prior to intubation and two puffs of NTG sub lingual spray (400 µg/spray) two minutes prior to intubation will significantly attenuate the hemodynamic response to endotracheal intubation in normotensive patients.

## 2. MATERIALS AND METHODS

Following institutional approval by the ethics committee at Mysore Medical College, Rajiv Gandhi University (Mysore, India), informed consent to participate in this study was obtained from 80 patients. The study population consisted of randomly selected ASA physical status I/II male/female adults between the ages of 18-60 yrs, who were scheduled for elective surgical procedures. There were no statistical demographic differences observed with respect to number of patients in each group (n=40), age or weight (Table 1), although both the study and control groups had a disproportionate female biased gender distribution. Patients having pre-existing systemic disorders such as ischemic heart disease, hypertensive heart disease, Diabetes mellitus, bronchial asthma, previous myocardial infarction, renal disease, cerebrovascular insufficiency or association with any co-morbid disease were excluded from the study.

|                | Gender ratio*<br>(M/F) | Age** [years]           | Weight** [kg]          |
|----------------|------------------------|-------------------------|------------------------|
| Control        | 10/30                  | 26.7±7.96/36.13±9.50    | 56.8±6.58/48.67±6.43   |
| Nitroglycerine | 16/24                  | 37.63±12.28/35.33±12.77 | 54.81±14.11/48.04±9.90 |

\*Randomly selected ASA Grade I/II patients (n=40)

\*\*Values represent means ± SD

**Table I.** Study participant demographic data

Each patient was randomly assigned to one of two double-blind study groups: the control group received a single IV bolus of fentanyl (2 µg kg<sup>-1</sup>) diluted to 5 mL with normal saline 5 minutes prior to laryngoscopy and intubation (n=40) and the study group received the same dose

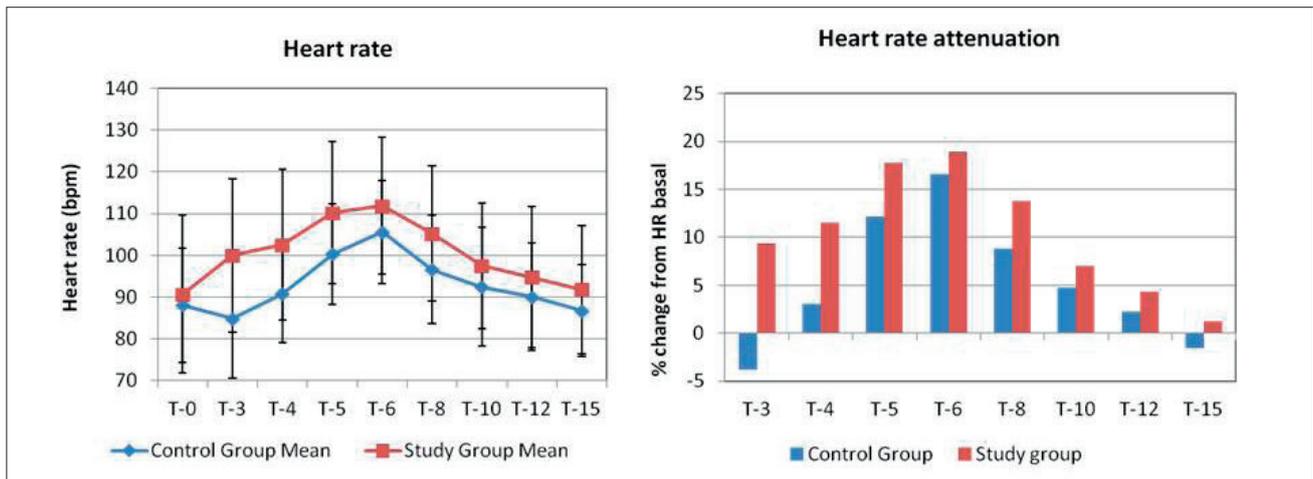
of fentanyl 5 minutes prior to intubation as well as two puffs of NTG sub lingual spray (400 µg /spray) 2 minutes before intubation (n=40). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded via a Siemens SC-7000 multi-channel monitor for each patient prior to administration of the study drug (T-0), 3 minutes after pre-oxygenation and study drug administration (T-3), induction (T-4), intubation (T-5), and at post-intubation time increments of 1-minute (T-6), 3-minutes (T-8), 5-minutes (T-10), 7-minutes (T-12) and 10-minutes after intubation (T-15). Rate Pressure Product (RPP) was also calculated and evaluated.

One day prior to surgery each patient underwent a thorough, pre-anesthetic evaluation with special consideration to a history of hypertension, Diabetes mellitus, chest pain, dyspnoea, convulsions, wheezing and myocardial infarction as well as previous anesthetic history and drug sensitivity. Patients meeting study criteria were advised to fast the night prior to surgery and were pre-medicated with a single oral dose of 150mg ranitidine and 0.5 mg alprazolam. On the day of surgery, patients were pre-medicated with a single injection of 0.2 mg glycopyrrolate and 2 mg midazolam given intramuscularly 30 minutes prior to surgery. After an infusion of dextrose normal saline, patients were connected to the Siemens multi-channel monitor. After recording baseline HR, SBP, DBP, and MAP levels (T-0), the fentanyl (2 µg kg<sup>-1</sup> of fentanyl diluted to 5 mL with normal saline) was administered and patients were pre-oxygenated for 3 minutes via a face mask with Bains circuit. At this point, after preoxygenation for 3 minutes, the NTG was administered to the experimental patients, but not to the control patients (T-3). Anesthesia was induced with thiopentone 5 mg/kg as a 2.5% solution and endotracheal intubation was facilitated with 1.5 mg/kg IV succinylcholine one minute prior to laryngoscopy and intubation (T-4). Laryngoscopy and intubation were performed and upon bilateral, equal air entry confirmation, the endotracheal tube was fixed and the patients were mechanically ventilated using a Bains system (T-5). HR, SBP, DBP, and MAP levels continued to be recorded up to 10 minutes post-intubation while anesthesia was maintained using 66% nitrous oxide and 33% oxygen mixture along with a neuromuscular blockade of 0.05 mg/kg vecuronium bromide. Anesthesia was reversed with 0.05 mg/kg neostigmine IV bolus and 0.02 mg/kg atropine IV bolus.

Summary statistics of patient gender, age, and weight for both the control (fentanyl) and experimental groups (fentanyl + NTG) were reported as means ± standard deviation (Table 1). Intra- and inter-group analysis for HR, SBP, DBP, MAP, and RPP were statistically evaluated using one-way ANOVA and Paired T-tests using both Microsoft® Office Excel and Minitab™ where p<0.05 was considered significant, and p<0.001 highly significant. While they were not reported in this article, paired F-tests were performed to further support the results of the T-tests.

## 3. RESULTS

A single pre-induction bolus injection of fentanyl in conjunction with two puffs of NTG in a thiopentone/suxame-



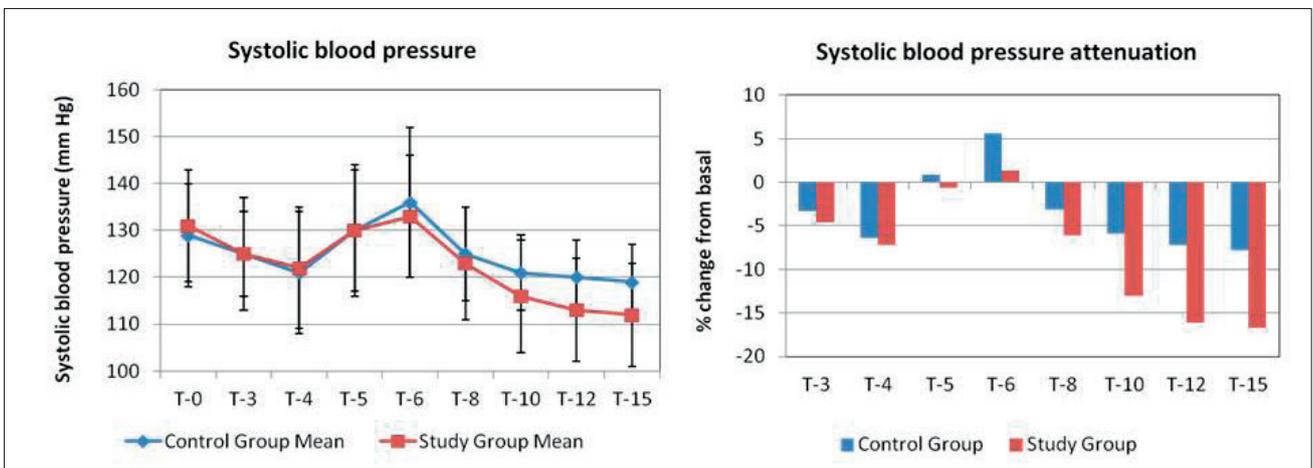
**Figure 1. A** – mean HR values for control and nitroglycerin-fentanyl groups ± SD and **B** – percent difference between measured HR levels and basal values.

thonium anesthetic sequence was observed in most cases to attenuate the hemodynamic pressor response resulting from endotracheal intubation in normotensive patients.

**Heart rate (HR)**

Acceleration of heart rate related hemodynamic response to tracheal intubation by a bolus of fentanyl and NTG spray was observed at all measured time points, that being a 7.9% greater average value than the control group (Figure 1A) and a 8.5% greater average value from NTG-fentanyl basal levels (Figure 1B). At pre-induction

heart rate for the NTG-fentanyl group only increased by 5.29% when compared to that of the control group which was not significant (T-10) ( $t=1.53, P=0.064$ ). Likewise, at 7 min after intubation the heart rate for the NTG-fentanyl group only increased by 5.06% when compared to that of the control group which was also not significant (T-12) ( $t=1.39, P=0.085$ ). At 10 min post-intubation the heart rate for the NTG-fentanyl group was 5.74% above that of the control group (T-15) ( $t=1.72, P=0.045$ ) which was significant.

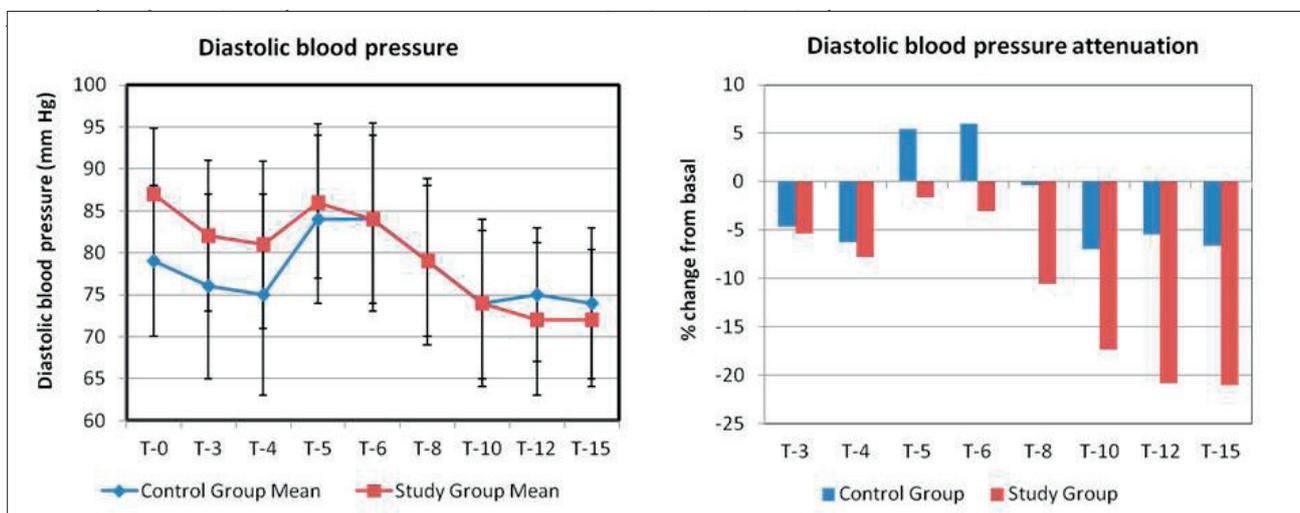


**Figure 2. A** – mean SBP values for control and nitroglycerin-fentanyl groups ± SD and **B** – percent difference between measured SBP levels and basal values.

(T-3), the NTG-fentanyl group was observed to have a 16.45% increase in heart rate as compared to the control group which was very statistically significant ( $t=4.15, P<0.001$ ). Likewise, induction values for the NTG-fentanyl group were 12.11% above those of the control group (T-4) which was also very significant ( $t=3.44, P<0.001$ ). At intubation (T-5), the NTG-fentanyl group was observed to have a 9.43% increase in heart rate as compared to the control group which is still statistically significant but not highly significant ( $t=3.00, P=0.002$ ). Further significant acceleration was also observed 1 min after intubation (T-6) ( $t=1.91, P=0.030$ ) which was higher than the control value by 5.73% and 3 min after intubation by 8.57% (T-8) ( $t=2.63, P=0.005$ ). However, at 5 min after intubation the

**Systolic blood pressure (SBP)**

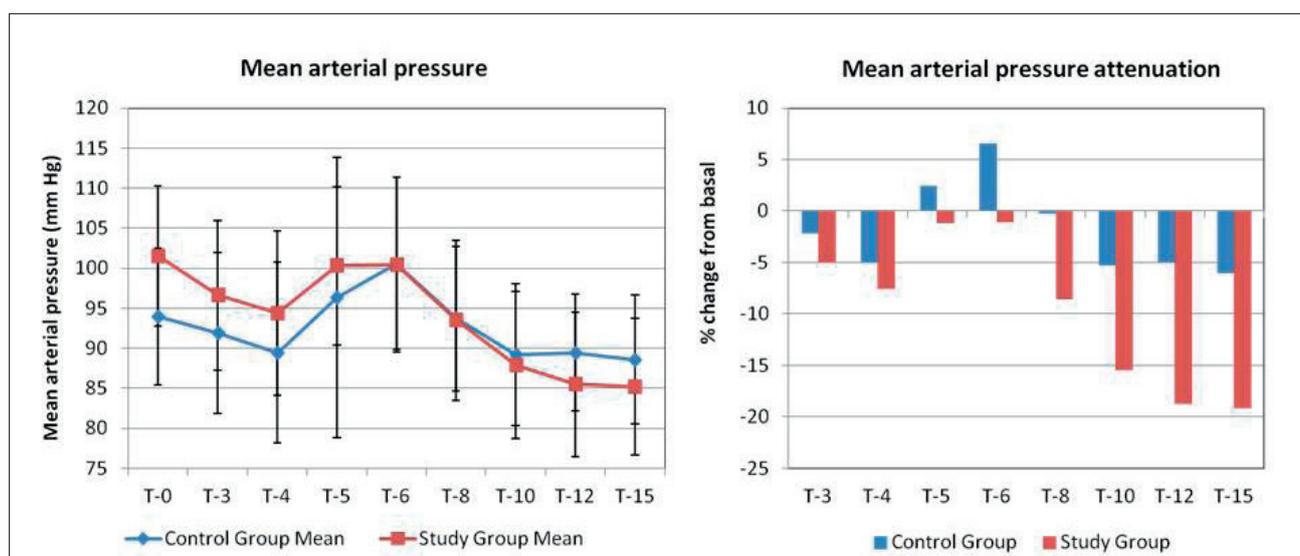
Attenuation was observed at some time intervals and acceleration was observed at other time intervals for systolic blood pressure in the NTG-fentanyl group with a 2.7% lower average value than the control (Figure 2A) and a 2.9% lower average value than the NTG-fentanyl basal value (Figure 2B). The greatest difference in systolic blood pressure between measured points was at 7 min after intubation (T-12) where a 6.36% decrease from control levels was observed in the NTG-fentanyl group that was highly statistically significant ( $t=3.38, P<0.001$ ) which was followed by a 6.33% decrease from control levels in the NTG-fentanyl group at 10 min post-intubation that was also highly significant (T-15) ( $t=3.38, P<0.001$ ).



**Figure 3. A** – mean DBP values for control and nitroglycerin-fentanyl groups  $\pm$  SD, **B** – percent difference between measured DBP levels and basal values.

There was also a 4.85% decrease of systolic blood pressure from control levels that was observed in the NTG-fentanyl group at 5 min post-intubation which was significant but not highly significant (T-10) ( $t=2.47$ ,  $P=0.008$ ). The differences in systolic blood pressure from control levels that were observed in the NTG-fentanyl group at all other times were not significant, three of those being increases of 0.32% at pre-induction (T-3) ( $t=0.16$ ,  $P=0.436$ ), 0.91% at induction (T-4) ( $t=0.38$ ,  $P=0.352$ ) and 0.08% at

for the NTG-fentanyl group when compared to control levels was observed at 7 min post-intubation (T-12) with a 4.32% difference but was not statistically significant ( $t=1.61$ ,  $P=0.055$ ). There were statistically significant DBP accelerations at the basal (T-0) ( $t=4.15$ ,  $P<0.001$ ) of 9.27%, at pre-induction (T-3) ( $t=3.04$ ,  $P=0.002$ ) of 8.60% and at induction (T-4) ( $t=2.52$ ,  $P=0.007$ ) of 7.80% for the NTG-fentanyl group when compared to control levels. All other values for the NTG-fentanyl group when com-



**Figure 4. A** – mean MAP values for control and nitroglycerin-fentanyl groups  $\pm$  SD, **B** – percent difference between measured MAP levels and basal values.

intubation (T-5) ( $t=0.03$ ,  $P=0.487$ ), and the other two being decreases of 2.73% at 1 min after intubation (T-6) ( $t=1.12$ ,  $P=0.133$ ) and 1.29% at 3 min after intubation (T-8) ( $t=0.62$ ,  $P=0.268$ ).

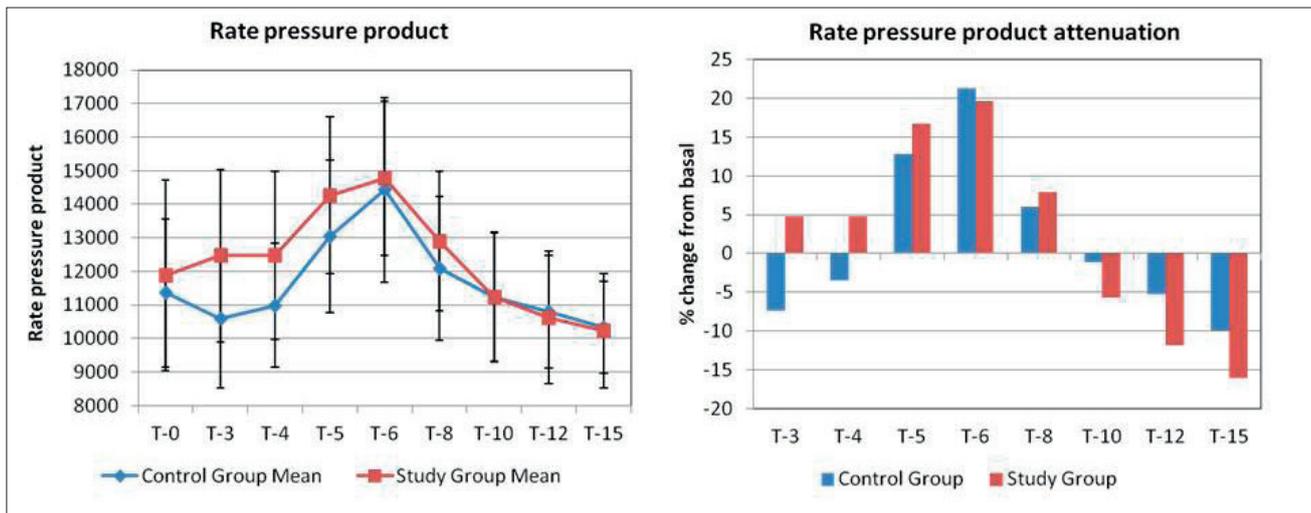
#### Diastolic blood pressure (DBP)

As with SBP, attenuation was observed at some time intervals and acceleration was observed at other time intervals for the DBP pressor response to intubation in the NTG-fentanyl group, that being a 4.0% greater average value than the control group (Figure 3A) and a 3.3% greater average value than NTG-fentanyl basal values (Figure 3B). There was not significant attenuation of DBP pressor response for the NTG-fentanyl group when compared to the control group. The greatest attenuation

pared to control levels were not statistically significant, two of those being increases of 2.13% at intubation (T-5) ( $t=0.82$ ,  $P=0.208$ ) and 0.12% at 1 min post-intubation (T-6) ( $t=0.04$ ,  $P=0.484$ ), and the rest being decreases of 0.32% at 3 min post intubation (T-8) ( $t=0.12$ ,  $P=0.454$ ), 0.03% at 5 min post-intubation (T-10) ( $t=0.01$ ,  $P=0.495$ ) and 3.42% at 10 min post-intubation (T-15) ( $t=1.26$ ,  $P=0.105$ ).

#### Mean arterial pressure (MAP)

Just like SBP and DBP, inter-group MAP values yielded attenuation at some time intervals and acceleration other time intervals in the NTG-fentanyl group when it was compared to control levels, that being a 3.6% greater average value than the control group (Figure 4A) and a 3.1% greater average value than NTG-fentanyl basal values



**Figure 5.** A – mean RPP values for control and nitroglycerin-fentanyl groups  $\pm$  SD, B – percent difference between measured RPP levels and basal values.

(Figure 4B). The greatest attenuation for the NTG-fentanyl group when compared to control levels was observed at 7 min post-intubation (T-12) with a 4.51% difference which was statistically significant ( $t=2.15$ ,  $P=0.017$ ). This was followed by another attenuation for the NTG-fentanyl group when compared to the control group at 10 min post-intubation (T-15) where the difference was 3.93% which was also statistically significant ( $t=1.84$ ,  $P=0.035$ ). There were statistically significant accelerations for the NTG-fentanyl mean when compared to control levels of 7.73% at the basal (T-0) ( $t=3.91$ ,  $P<0.001$ ), 4.97% at pre-induction (T-3) ( $t=2.16$ ,  $P=0.017$ ) and 5.38% at induction (T-4) ( $t=2.05$ ,  $P=0.022$ ). There was also a statistically insignificant acceleration for the NTG-fentanyl mean when compared to control levels of 4.08% at intubation (T-5) ( $t=1.26$ ,  $P=0.106$ ). Insignificant attenuation was observed at all other time intervals for the NTG-fentanyl group when compared with control levels, those being 0.13% at 1 min post-intubation (T-6) ( $t=0.05$ ,  $P=0.478$ ), 0.24% at 3 min post-intubation (T-8) ( $t=0.11$ ,  $P=0.458$ ) and 1.47% at 5 min post-intubation (T-10) ( $t=0.64$ ,  $P=0.261$ ).

#### Rate pressure product (RPP)

The rate pressure product was similar to HR at earlier time intervals but closer SBP values at later time intervals with regards to percent difference between control and NTG-fentanyl groups. When compared to control levels, a 6.0% greater average value was observed in the NTG-fentanyl group (Figure 5A) and a 6.2% greater average value to NTG-fentanyl basal values (Figure 5B). As with SBP, the greatest attenuation was observed at 7 min post-intubation (T-12) with a NTG-fentanyl group mean of 1.62% below that of the control group, but unlike SBP, this value was not statistically significant ( $t=0.42$ ,  $P=0.337$ ). This was followed by further attenuation for the NTG-fentanyl group when compared to the control group at 10 min post-intubation (T-15) where the difference was 0.95% which was statistically insignificant ( $t=0.28$ ,  $P=0.390$ ). For all other values, the NTG-fentanyl mean was greater than that of the control group, those being a statistically insignificant increase of 4.46% at the basal (T-0) ( $t=0.91$ ,  $P=0.182$ ), a very significant increase of 16.37% at pre-induction (T-3) ( $t=3.63$ ,  $P<0.001$ ), a significant

increase of 12.76% at induction (T-4) ( $t=3.05$ ,  $P=0.002$ ), another significant increase of 8.99% at intubation (T-5) ( $t=2.38$ ,  $P=0.010$ ), an insignificant increase of 2.32% at 1 min post-intubation (T-6) ( $t=0.60$ ,  $P=0.277$ ), a significant increase of 6.45% at 3 min post intubation (T-8) ( $t=1.71$ ,  $P=0.046$ ) and an insignificant increase of 0.05% at 5 min post intubation (T-10) ( $t=0.01$ ,  $P=0.495$ ).

#### 4. DISCUSSION

The goal of this study was to investigate the relative effectiveness of the combined use of fentanyl with NTG to mitigate hemodynamic pressor response caused by endotracheal intubation. Previously, it has been shown that timed delivery of low doses of fentanyl can somewhat counterbalance the short lasting elevation in HR, SBP, DBP, MAP, and RPP that result from endotracheal intubation (8, 16). However, the use of fentanyl alone was not sufficient to completely suppress hemodynamic pressor changes. NTG was chosen to be used in conjunction with fentanyl due to its ability to slowly decrease blood pressure and low dosage requirements. The mechanism of action for opioids like fentanyl includes the activation of the nitric oxide (NO)/cyclic-guanosine monophosphate (cGMP) pathway. Consequently, the introduction of an additional NO source might increase effectiveness (15). Theoretically, NTG could serve as this additional NO source thus possibly increase the effectiveness of fentanyl in attenuating the hemodynamic response during intubation.

A successful test would at least show better suppression of hemodynamic pressor response than fentanyl alone and ultimately would show no variation from basal measurements. However, for most of the measured hemodynamic parameters in our study, we concluded that the attenuation observed using the fentanyl-NTG combination was at best comparable to if not less effective than the use of fentanyl alone. We also observed some hemodynamic instability. At all time intervals T-3 through T-15 when HR was measured and some time intervals for DBP, MAP and RPP, the values for the experimental fentanyl-NTG group were higher than those of the control fentanyl only group. This suggests that the use of NTG in conjunction with fentanyl actually reduced the overall suppressive effectiveness of fentanyl on these hemodynamic parameters at specific time intervals. However, there were time intervals for SBP and MAP where the values for the fentanyl-NTG group were lower than the fentanyl

only group and in some cases dropped significantly below the basal level. This suggests that the use of NTG in conjunction with fentanyl increased the overall suppressive effectiveness of fentanyl on SBP and MAP at specific time intervals. The variations in hemodynamic pressure responses to endotracheal intubation that were observed during this study for certain hemodynamic parameters at certain time intervals could be due to antagonistic drug interaction, overlapping duration of action, or experimental error or bias. There were also some time intervals for SBP, DBP, MAP and RPP where the hemodynamic values for the control and experimental groups were statistically equivalent, indicating that in those cases NTG neither increased nor decreased the effectiveness of fentanyl to reduce hemodynamic pressor response.

Other studies have also reached conclusions that were similar to our study's findings when attempting to use fentanyl and NTG to attenuate hemodynamic pressor responses. A study found that when used in combination with NTG or phenylphrine, fentanyl did not induce any significant changes in HR or SBP (17). In a clinical trial where NTG was used in combination with fentanyl and pancuronium for anesthesia, the hemodynamics of the fentanyl-pancuronium and placebo groups were statistically identical after induction [18]. Another study also concluded that combining NTG with fentanyl and pancuronium failed to attenuate hemodynamic pressor responses when the NTG dosage was  $.5 \mu\text{g}^*\text{kg}^{-1}*\text{min}^{-1}$ . However, this study also concluded that at a NTG dosage of  $1 \mu\text{g}^*\text{kg}^{-1}*\text{min}^{-1}$ , there were modest but significant decreases in systolic and diastolic blood pressure during skin incision (19, 20, 21). A study that compared the hemodynamic effects of fentanyl to ketamine when combined with propofol found that fentanyl caused hypotension during induction and alleviated stress-response during laryngoscopy and intubation. That study also reported an increase in blood pressure and pulse rate during the maintenance phase (22). At least at certain dosages, these studies support the conclusion from our study that fentanyl and NTG can cause hemodynamic instability.

In the future, further testing could focus on using other drugs in conjunction with fentanyl and NTG as well as different dosages and methods for the infusion of these drugs into the patient. With the proper dosage of NTG and fentanyl along with other drugs that could be useful during anesthesia, methods can be developed for infusing these drugs into the patients that could result in significant attenuation of hemodynamic pressor responses. There have been some clinical trials where NTG and fentanyl were used in combination with other drugs at different dosages and the results were encouraging. At a NTG dosage of  $1 \mu\text{g}^*\text{kg}^{-1}*\text{min}^{-1}$ , fentanyl and pancuronium have been successful in attenuating hemodynamic pressor responses, which resulted in a decrease in intraoperative ischemic episodes (19, 20, 21). A study that compared the use of fentanyl and NTG in Thoracic epidural anesthesia (TEA) to general anesthesia found significant attenuation of HR and MAP during TEA (23). The hemodynamic effects of other drugs such as clonidine, bupivacaine and gabapentin when used in combination with fentanyl or NTG could also be investigated. It was found that clonidine and oral gabapentin attenuated the hyperdynamic response following laryngoscopy and intubation [24]. When varying dosages of fentanyl, clonidine and bupivacaine were used in combination with each other for anesthesia, it was found that they produced a low pain score with few side effects (25). There clearly remains a lot

of potential for the use fentanyl and NTG in improving anesthesia. When administered through the proper dosage, anesthesia method and combination of drugs, fentanyl and NTG could be used to acquire better hemodynamic results than the ones obtained in our study. There were no statistical demographic differences observed with respect to number of patients in each group (n=40), age or weight, although both the study and control groups had a disproportionate gender distribution.

## CONFLICT OF INTEREST: NONE DECLARED.

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