

## The Effect of Peri-Radial Injection of Papaverine Versus Nitroglycerine on Radial Artery Diameter Prior to Cannulation

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### ABSTRACT

**Objective:**The present study aimed to compare the effect of periradial injection of Papaverine versus Nitroglycerine on radial artery diameter prior to cannulation in cardiac surgery patients.

We hoped that periradial injection will facilitate the radial artery cannulation and decrease its spasm.

**Design:**This is a prospective randomized controlled trial that included ninety patients scheduled for elective cardiac surgery.

**Interventions:**Patients were randomly assigned into one of three groups: One group received a peri-radial subcutaneous injection of Papaverine and Lignocaine 2% (30 participants); the second group received a peri-radial subcutaneous injection of Nitroglycerine and Lignocaine 2% (30 participants) and a control group that received a peri-radial subcutaneous injection of Lignocaine 2% (30 participants).

**Measurements and Main Results:**The radial artery diameter was measured by ultrasound before the injection and 20 minutes following injection, and the radial pulse palpability score was measured on a score of 1 (being weak) to 3 (being strongly palpable) before the injection and 20 minutes after. We observed a significant increase in radial artery diameter after injection of Papaverine ( $p < 0.001$ ) and Nitroglycerine ( $p < 0.001$ ), compared to baseline values, while there was no significant change in the control group. The changes in the Papaverine group were significantly higher ( $p = 0.003$ ) than that observed in the Nitroglycerine group. The palpability score of the radial artery was significantly higher in the Papaverine group than the Nitroglycerine group and both are significantly higher than the control group.

**Conclusions:**Papaverine achieved significant increases in radial artery diameter and palpability score.

**Keywords:** Radial artery, Papaverine, Nitroglycerine.

### INTRODUCTION

Arterial cannulation is a routine pre-operative procedure, performed in cardiac surgery for continuous monitoring of blood pressure and repeated arterial blood sampling [1-3]. In cardiac surgery, the radial artery is the best site for cannulation, compared to other vessels because it is easy to find and its cannulation is usually smooth without complications [1]. However, cannulation of the radial artery is sometimes difficult because it is susceptible to arterial spasm that may occur in the traumatic puncture. Moreover, the radial artery has a large muscular layer with a small diameter and marked receptor-mediated vasomotion [4].

To decrease the radial spasm, various vasodilators are used like nitrates [5] and calcium channel blockers [6]. In addition, papaverine, an alkaloid obtained from opium or prepared synthetically, is a vasodilator that is used to resolve the radial artery spasm during coronary angiography [7].

During coronary artery bypass surgery, papaverine increases the internal mammary artery blood flow [8]. In addition, recent data showed that radial artery diameter and pulse palpability are significantly increased after subcutaneous papaverine injection, which would facilitate the cannulation procedure [9].

Nitroglycerine is a vasodilator of low cost, short half-life, and few adverse effects [10]. Administration of nitroglycerin by different routes (intravenous [11], topical [12], and intra-arterial [13]) has been proven to cause vasodilatation of the radial artery. Further, recent data indicate that subcutaneous injection of nitroglycerin dilates the radial artery [14]. Therefore, we performed this study to assess the effect of periradial injection of papaverine versus nitroglycerine on radial artery diameter prior to cannulation.

### Methodology:

This was a prospective randomized controlled trial that enrolled 90 patients scheduled for elective cardiac surgery.

Patients were randomly assigned into one of three groups: One group received a peri-radial subcutaneous injection of papaverine and lignocaine 2% (30 participants); the second group received a peri-radial subcutaneous injection of nitroglycerine (1mg/ml) and lignocaine 2% (30 participants) and a control group that received a peri-radial subcutaneous injection of lignocaine 2% (30 participants). Randomization and blinding were performed using a closed opaque envelope.



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We included any patient in the age range from 20 years to 55 years scheduled for elective cardiac surgery and was hemodynamically stable. We excluded patients with negative modified Allen test, arterioventricular block, hypotension, glaucoma, altered liver function, unstable hemodynamics, emergency surgeries, and peripheral vascular disease, also elderly patients more than 55 years were excluded for fear of vascular sclerosis which makes their vessels insensitive to vasodilators.

The solution for the first group comprised 1 ml papaverine (30 mg/ ml) and 1 ml lignocaine 2%, while the solution in the second group comprised 1 ml nitroglycerine and 1 ml lignocaine 2%. The control group patients received 1 ml of normal saline and 1 ml of lignocaine 2%. The injections were prepared by a research assistant in a covered syringe to ensure the physician blinding to the color of the drug. The injections were done slowly, 1 cm proximal to the styloid process of the radial bone.

The radial artery diameter was measured by a linear ultrasound transducer (10-12MHz) before the injection and 20 minutes following injection. One operator, blinded to the injection ingredients, performed the measurements in all patients. The radial pulse palpability score was measured on a score of 1 (being weak) to 3 (being strongly palpable) before the injection and 20 minutes after. Further, another blinded physician measured the heart rate (HR) and the mean arterial pressure (MAP) before injection and 20 min later.

**Ethical Considerations**

All participants signed informed consent forms for participation in the study. The study was approved by the Ethical Committee of Beni-Suef University, (FM-BSU REC #FWA00015574/3-2-2019) and registered in clinical trials government. We followed the World Medical Association's Ethical Code for human experimentation (Helsinki Declaration).

**Statistical analysis**

We used the Statistical Package for Social Sciences (Version 22 for PC, IBM Inc, Armonk, NY) to perform the analysis. Data were reported as frequencies (%) if categorical and means ± SD if numerical. We employed the one-sample t-test to measure the differences before and after injection in the same group. The ANOVA test with the posthoc Bonferroni test was used to compare the changes in the three enrolled groups. A p-value less than 0.05 was considered statistically significant.

**RESULTS**

We observed that there was no significant difference between the papaverine, nitroglycerine, and control groups in terms of age ( $p = 0.25$ ) and gender ( $p = 0.72$ ). Table 1 summarized the baseline characteristics in the three enrolled groups.

**Table (1):** Demographics of papaverine, nitroglycerine, and Control groups

Demographics		Papaverine group (n=30)	Nitroglycerine group (n=30)	Control Group (n=30)	P-value
Age in years ± SD		49.23 ± 11.95	51.53 ± 12.21	54.07 ± 9.29	0.254
Sex	Male [n (%)]	19 (63.3%)	18 (60%)	16 (53.3%)	0.725
	Female [n (%)]	11 (36.7%)	12 (40%)	14 (46.7%)	

As regarding the Radial artery diameter and palpability, we observed a significant increase in radial artery parameters after injection of papaverine ( $p < 0.001$ ) and nitroglycerine ( $p < 0.001$ ), compared to baseline values. However, no significant difference was observed in the control group ( $p = 0.76$ ). Moreover, the change observed in the papaverine group was significantly higher ( $p = 0.003$ ) than that observed in the nitroglycerine group and was higher in both intervention groups (papaverine and nitroglycerine than control).

Similarly, regarding radial artery palpability score, we observed significant increases in the papaverine ( $p < 0.001$ ) and nitroglycerine ( $p < 0.001$ ) groups, while the control group showed no significant difference ( $p = 0.16$ ). In addition, the change observed in the papaverine group was significantly higher ( $p = 0.001$ ) than the nitroglycerine group and both interventions groups had post-injection radial palpability scores that were higher than the control group; Table 2.

**Table (2):** Clinical parameters in the study groups before and after injection

Clinical parameters		Before Injection [mean ±SD]	After injection [mean ±SD]	P-value	P-value Between Groups
<b>Radial artery Diameter</b>	Papaverine group	2.21 ± 0.15	2.44 ± 0.14	<0.001*	0.003*
	Nitroglycerine group	2.21 ± 0.13	2.34 ± 0.15	<0.001*	
	Control group	2.197 ± 0.14	2.2 ± 0.15	0.763	
<b>Pulse palpability Score</b>	Papaverine group	1.7 ± 0.6	2.77 ± 0.43	<0.001*	0.001*
	Nitroglycerine group	1.53 ± 0.57	2.67 ± 0.48	<0.001*	
	Control group	1.7 ± 0.53	1.83 ± 0.7	0.161	
<b>HR</b>	Papaverine group	86.27 ± 10.34	87.43 ± 9.12	0.117	0.625
	Nitroglycerine group	83.93 ± 8.64	86.17 ± 7.27	0.004*	
	Control group	83.53 ± 10.52	86.13 ± 8.09	0.006*	
<b>MBP</b>	Papaverine group	90.4 ± 5.14	92.13 ± 5.05	0.001*	0.11
	Nitroglycerine group	93.27 ± 6.1	93.4 ± 6.17	0.884	
	Control group	94.03 ± 6.84	94.63 ± 6.83	0.492	

The hemodynamics parameters measured showed no significant increase in heart rate in the papaverine group (p= 0.11), while we observed significant increases in the nitroglycerine (p= 0.004) and control groups (p= 0.006). However, comparing the HR change between the papaverine and nitroglycerine groups, we recorded no significant difference (p= 0.62).

Regarding the mean blood pressure, we observed a significant increase in the papaverine group (p= 0.001), while no significant change was observed in the nitroglycerine (p= 0.88) and control groups (p= 0.49). Similarly, no significant difference was noted (p= 0.11) among the three groups.

**DISCUSSION**

This randomized study was aimed to compare the efficacy of papaverine versus nitroglycerine in facilitating the cannulation of the radial artery before cardiac surgery.

We found that papaverine significantly increases the radial artery diameter and palpability score, compared to nitroglycerine, which would indicate more facilitation of radial artery cannulation. Moreover, papaverine can be considered safe in terms of systemic effects; the increase in HR was not significant and was less than nitroglycerine. While the observed increase in MBP with papaverine was statistically significant, it is likely not clinically significant (almost 2 mmHg). Moreover, the comparison between papaverine and nitroglycerine did not find a significant difference, which further confirms our point of view on the safety of papaverine in this regard.

To explain the vasodilatory properties of papaverine, several mechanisms for its smooth muscle relaxing effects have been reported. First, it inhibits the phosphodiesterase enzyme, which increases the smooth muscle concentration of cyclic adenosine monophosphate

(cAMP). Moreover, it significantly decreases the calcium influx into the smooth muscle cell. In addition, papaverine inhibits the release of calcium from intracellular stores<sup>[9]</sup>.

Our results are in agreement with a former study by **Nagaraja et al.** who showed significant increases in radial artery diameter and palpability score after the injection, compared to baseline values. Using a similar dose to the one used in the present study, they also found no significant change in HR and MAP following the injection<sup>[9]</sup>. However, our study is the first to compare papaverine to nitroglycerine in that regard. Another study by **Osman et al.** showed marked efficacy for intra-arterial papaverine injection in resolving severe radial artery spasm during radial cardiac catheterization<sup>[7]</sup>. On the other hand, **Mussa et al.** compared verapamil/nitroglycerin, phenoxybenzamine, and papaverine as topical antispasmodics for radial artery CABG. They found that papaverine had limited antispasmodic activity and the shortest duration of action of the three tested agents<sup>[15]</sup>.

Former studies have also examined the effects of papaverine on endothelial integrity. He found that verapamil plus nitroglycerine preserved the endothelial function in 25 radial artery segments taken from patients undergoing CABG, while papaverine impaired this function<sup>[16]</sup>. **Wegrzyn** and colleagues reported that radial artery segments exposed to papaverine (2 mg/ml in vitro) showed more vasodilatation, but yet more endothelial damage than segments exposed to papaverine at a concentration of 0.5 mg/ml<sup>[17]</sup>.

This study, however, has some limitations. First, the sample size in individual arms is admittedly small. However, this was equivalent to a power of 80% in our sample size calculation and it was stated in our registered protocol (NCT04030663). Moreover, we did not assess the effects of papaverine on some parameters as endothelial integrity and duration of action. Our study followed the patients only intra-operatively and our main focus was the efficacy of papaverine in achieving the intended purpose in comparison to nitroglycerine. Future studies should enroll a larger sample size and pay more attention to the aforementioned outcomes.

In conclusion, the current study showed that papaverine achieved significant increases in radial artery diameter and palpability score in comparison to nitroglycerine with almost similar systemic vascular effects. Future studies should confirm these findings, using larger sample sizes and longer follow-up periods.

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