How to Cite:
Kangralkar, G., Dhulkhed, V. K., & Gandhi, S. (2022). Comparative evaluation of the hemodynamic effects of inclusion versus exclusion of dexmedetomidine to pregabalin and fentanyl premedication regimen during airway instrumentation in laparoscopic abdominal surgeries. *International Journal of Health Sciences*, *6*(S2), 10159–10168. https://doi.org/10.53730/ijhs.v6nS2.7725

Comparative evaluation of the hemodynamic effects of inclusion versus exclusion of dexmedetomidine to pregabalin and fentanyl premedication regimen during airway instrumentation in laparoscopic abdominal surgeries

Dr. Gouri Kangralkar
Postgraduate student, Department of Anesthesiology, Krishna Institute of Medical Sciences, Karad (Deemed to be University), Maharashtra, India

Dr. V. K. Dhulkhed*
Professor, Department of Anesthesiology, Krishna Institute of Medical Sciences (Deemed to be University), Karad, Maharashtra, India
*Corresponding author

Dr.Soudamini Gandhi
Assistant Professor, Department of Anesthesiology, Krishna Institute of Medical Sciences (Deemed to be University),

***Abstract*---**Background: Airway instrumentation leads to an aggravated hemodynamic response due to increased sympathetic activity, imposing a risk of myocardial ischemia. A premedication regimen using fentanyl and pregabalin blunts the pressure response but not the rate response. Objective: To compare the effects of pregabalin and fentanyl regimen versus pregabalin, fentanyl, and dexmedetomidine regimen on the hemodynamic pressor response during airway instrumentation in laparoscopic abdominal surgery (LAS). Methods: Sixty patients (ASA I and II), undergoing elective LASunder general anesthesia, were randomly divided into 2 groups - Group A (n=30) premedicated with oral pregabalin (150mg) and IV fentanyl (2µg/kg) and Group B (n=30) premedicated with IV dexmedetomidine (0.25µg/kg) in addition to pregabalin-fentanyl regimen. Both groups were managed with the same anesthetic protocol. The preoperative sedation level was assessed before induction. The heart rate (HR), systolic and diastolic BP (SBP, DBP), and mean arterial pressure (MAP) were recorded at baseline as well as

Manuscript submitted: 27 March 2022, Manuscript revised: 18 April 2022, Accepted for publication: 9 May 2022

preoperatively, prior to intubation and at 1, 3, 5, 10, and 15 min after intubation. Results: Both groups had similar distribution of age, weight, gender, physical status, sedation level as well as intra-operative fentanyl and postoperative analgesic requirements. All the four hemodynamic parameters (HR, SBP, DBP, and MAP) were significantly greater in Group A than Group B ($p<0.001$). Conclusion: Addition of low-dose dexmedetomidine (0.25µg/kg) to the pregabalin and fentanyl premedication regimen is associated with greater blunting of HR and BP responses to airway instrumentation in laparoscopic abdominal surgeries, compared to pregabalin and fentanyl without dexmedetomidine.

***Keywords*---**laparoscopy, intratracheal intubation, laryngoscopy, premedication.

Introduction

Laparoscopic abdominal surgery (LAS), performed under general anesthesia, is associated with an aggravated hemodynamic response, mainly due to airway instrumentation (AI), carbon dioxide (CO_2) insufflation, and anxiety.(1-4) Laryngoscopy and endotracheal intubation involving noxious stimulation of the tongue base, pharynx, larynx, and trachea are known to cause a reflex increase in the sympathoadrenal activity, resulting in an elevation in plasma catecholamines.(1,2) Use of CO_2 for insufflation leads to increasedintra-abdominal pressure (pneumoperitoneum) that compresses the inferior vena cava, causing reduction in the venous return and cardiac output as well as an increase in the systemic vascular resistance. This is also associated with an elevation in the circulating catecholamines.(3) Surgical anxiety is also associated with increased sympathetic activity to prepare the body for emergency.(4) This leads to an increase in the heart rate (HR) and blood pressure (BP), although transient, imposing a risk of myocardial ischemia, infarction, arrhythmias, and cardiac failure.(5,6)

Hence, preoperative sedation and cardiovascular stability are essential during induction, AI, and surgery for better patient outcome. Various strategies such as lesser duration of laryngoscopy, lidocaine sprays, opioids, α-2 agonists, and deeper planes of anesthesia using intravenous (IV) and inhalational agentshave been implemented to blunt the hemodynamic pressor response.(7) A common premedication regimen includes the use of fentanyl (analgesicpure µ-opioid receptor agonist with a rapid and a short duration of action) as well as pregabalin (analgesic, anticonvulsant, and anxiolytic gabapentinoid that decreases the synthesis of neurotransmitter glutamate to act on the central nervous system), which blunt the pressure response but not the rate response.(8,9) Addition of dexmedetomidine (a novel α-2 agonistic sedative) could provide better hemodynamic stability since it provides sympatholysis, attenuating both pressure and rate responses, along with the prevention of respiratory depression and reduction of intra- and post-operative analgesic requirement.(10) Therefore, the objective of this study was to compare the effects of premedication with pregabalin and fentanyl regimen versus pregabalin, fentanyl, and dexmedetomidine regimen on the hemodynamic pressor response during airway instrumentation in LAS.

Materials and Methods

This double-blind, prospective, randomized, controlled clinical study was conducted at the Department of Anesthesiology, Private Institute of Medical Sciences, XXX, from October 2017 to May 2019, after obtaining ethical clearance from the Institutional Review Board. Sixty patients aged 20-60 years, irrespective of gender, belonging to American Society of Anesthesiologists (ASA) physical status I and II, and undergoing elective LAS under general anesthesia were recruited into the study after obtaining written informed consent from them. Patients with history of hypertension, diabetes, impaired liver or kidney function, drug abuse, regular use of analgesics, chronic pain, and known hypersensitivity to the drugs used in this study, neurological deficits, and inability to verbally express pain severity, emergency surgeries, and pregnant women were excluded from the study.

Sixty patients who fulfilled the inclusion criteria were selected randomly using computer-generated random numbers and were equally and randomly divided using the sealed envelope system into 2 groups: Group A (n = 30) which received pregabalin tablet 150mg orally (1 h prior to surgery) and IV fentanyl 2μg/kg (10 min prior to surgery); and Group B (n = 30) which received pregabalin tablet 150mg orally (1 h prior to surgery), IV fentanyl 2μg/kg, and IV dexmedetomidine 0.25μg/kg as a 2-min infusion (both 10 min prior to surgery). Preoperative assessment was done for each patient, including complete hemogram, bleeding time and clotting time, blood sugar, serum electrolytes, kidney function tests, routine urine analysis, chest x-ray (postero-anterior view), and electrocardiogram.
Treatment procedure -All patients were kept nil per orally and not given analgesics within the 12-h preoperative period. Oral pregabalin (150mg) was given to all patients 1 h prior to the surgery. On arrival into the operation theater, a 20-gauge cannula was inserted into a vein on the dorsum of the patient's non-dominant hand and lactated Ringer's solution infused. Basal vital parameters like HR, systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO_2) were recorded. Thepreoperative sedation level was assessed using Ramsay Sedation Scale.[11] All patients were premedicated with IV fentanyl (2μg/kg) 10 min prior to laryngoscopy and intubation. Additionally, IV dexmedetomidine (0.25μg/kg) was administered as a 2-min infusion to Group B patients only, which was prepared for infusion by diluting 0.5mL dexmedetomidine (containing 50μg of the drug) with normal saline upto 12.5 mL (final concentration 4μg/mL). An equal amount of normal saline was given to Group A patients at the same rate. Patients were induced followed by the insertion of the laryngoscope and intubation. Ventilation was maintained at a tidal volume of 7-10 mL/kg, frequency of 12-15 breaths/min, and end-tidal CO_2 (Et CO_2) of 30-40 mmHg in 3L/min of fresh gas flow with 66% nitrous oxide in oxygen in a closed circuit. All intubations were accomplished within 15 s. Only those intubations accomplished within a single attempt were included in the study. Patients who coughed or bucked during the procedure were excluded. Parameters like HR, SBP, DBP, MAP, and SpO_2 were recorded preoperatively, prior to intubation, as well as 1, 3, 5, 10, and 15 min after intubation. Intraoperative requirements of fentanyl (20μg) top-ups were noted. Postoperative requirement of

analgesia (frequency and dose) up to 24 h after intubation was noted using a visual analogue scale (VAS) (Figure1). After intubation, patients were maintained on inhalation agents and non-depolarizing muscle relaxants. At the end of the surgery, they were reversed with IV glycopyrrolate and IV neostigmine and were shifted to the recovery room and monitored. IV diclofenac (75mg) was used as a rescue analgesic in the postoperative period if the VAS score was ≥4.

Statistical analysis -To detect a mean BP change of 15 mmHg with a standard deviation of 15mmHg for an alpha value of 0.05 and a power of 90%, considering a 10% dropout rate, a sample size of 30 patients per group was selected. Data was collected, compiled, and analyzed using statistical software SPSS version 20.0 (IBM Corp. Released 2011, IBM SPSS Statistics for Windows, and Version 20.0. Armonk, NY: IBM Corp.) And Microsoft Excel (Microsoft Corporation. Microsoft Excel [Internet] 2018. Available from: https://office.microsoft.com/exce). Descriptive and inferential statistical analysis was done. The categorical factors were represented by the number and frequency (%) of cases. The continuous variables were represented by measures of central frequency (like mean) and deviation (standard deviation and range) wherever appropriate. Statistical analysis was done by unpaired student's *t*-test, Mann-Whitney test, univariate analysis of variance, and general linear model for repeated measure. A P value <0.05 was considered as statistically significant.

Results

The study comprised 60 patients allocated into two groups, with a mean age of 33.07 ± 10.61 years in Group A and 32.16 ± 11.09 years in group B, with most patients in the 20-29 years age range. Both the groups had more females and the same M: F ratio (>90% of the patients had a BMI in the range of 19-25kg/m^2). The predominant ASA status was Grade I in both the groups (86.67%). Both groups were uniform in their distribution of age, weight, gender, and physical status, with no coexisting disease (Table 1).

In Group B, the Ramsay Sedation Score prior to intubation was greater as compared to Group A. After premedication in Group A, 76% (23/30) had a sedation score of 2 and 24% had a score of 3; where as in Group B, 50% (15/30) had a sedation score of 2 and the remaining 50% had a score of 3.Comparable Ramsay Sedation Scores were seen in both the groups. The frequencies of intraoperative fentanyl top-up requirements as well as postoperative analgesic requirements were also similar in both the groups. The demographic and medical characteristics of the study participants are presented in Table1. Changes in the mean HR, mean SBP, mean DBP, and MAP (recorded preoperatively, prior to intubation as well as 1, 3, 5, 10, and 15 min after intubation), analyzed using general linear mixed-effect model are summarized in Graphs1 to 4. The random effect for time and individual (subjects) was considered. All the four hemodynamic parameters were significantly greater in Group A than Group B, with p=0.00029 (for HR) and p<0.001 (for SBP, DBP, and MAP).

Discussion

This study was conducted to compare the hemodynamic effects of including versus not including dexmedetomidine to the pregabalin and fentanyl premedication regimen during airway instrumentation in laparoscopic abdominal surgeries. It was observed that the addition of dexmedetomidine to the regimen led to blunting of pressure as well as rate response, as evidenced by a flatter trend (Figures 1 to 4), compared to only pressure response attenuation seen with pregabalin and fentanyl without dexmedetomidine. There were no adverse cardiovascular effects seen with these drugs.

Scheinin et al also noted that dexmedetomidine attenuated the increase in the HR in response to airway instrumentation, with a maximum increase in HR being 6% with dexmedetomidine compared to 21% in the present study. This difference could be due to the use of a higher dose of dexmedetomidine (0.6µg/kg) and diazepam (0.2mg/kg) as premedication by Scheininet al, whereasthe present study did not employ diazepam. (12) Similar results were also recorded by Jaakola et al.(13) Lawrence et al reported that a single dose of 2µg/kg of dexmedetomidine prior to induction of anesthesia reduced the pressor response to intubation. However, there was bradycardia observed during the 1st and 5th min after administration, possibly due to the higher dose given as a bolus administration. In the present study, there was no incidence of bradycardia, perhaps because a smaller dose of dexmedetomidine (0.25µg/kg) was used as a 2-min infusion, rather than a higher bolus dose. (14) Keniya et alalso observed that the increase in HR after intubation was 7% with dexmedetomidine, whereas it was 21% in the present study which could be because Keniyaet al had used midazolam as a premedication in their study.(15)

The mean SBP, DBP, and MAP were better maintained during the intraoperative period with the use of dexmedetomidine than without it, similar to the findings of Hazra et al. (16) Jaakola et al too found a significant reduction in BP with 0.6µg/kg dexmedetomidine. (13) Some studies even observed that dexmedetomidine in low doses (0.25-1µg/kg) led to a reduction in the MAP but high doses (14µg/kg) led to atransient elevation in MAP. (17, 18)

Bloor et al (17) also reported that lower doses of dexmedetomidine (0.25µg/kg and 0.5µg/kg) resulted in a monophasic reduction in the mean BP, whereas higher doses (1-2µg/kg) resulted in biphasic responses (early transient pressor effect associated with doubling of the systemic vascular resistance and reduction in the cardiac output followed by longer lasting reduction in mean BP along with reduction in the cardiac output and HR). In the present study, there was no biphasic BP response observed, which suggests that transient pressor response can be prevented by slow infusion rate, which is also beneficial in patients with impaired cardiac function. (17)

The present research used a multi-drug approach so as to use these drugs at lower doses, thus reducing their side effects such as respiratory depression associated with high doses of fentanyl, which was not seen with dexmedetomidine. (19, 20) However, dexmedetomidine addition did not potentiate intraoperative and postoperative analgesic requirements, in contrast to the studies of Schienen et al, Keniya et al, and Bajwa et al who showed that dexmedetomidine reduced the postoperative analgesic requirement. This difference could be due to higher dosesof dexmedetomidine (0.6-1µg/kg) and diazepam (0.2mg/kg) used by them for premedication, compared to the present study (12, 15, 21)

This study establishes that dexmedetomidine addition to fentanyl-pregabalin premedication regimen provides better hemodynamic stability, both in terms of rate and pressure, along with prevention of respiratory depression, compared to fentanyl-pregabalin only.

However, this study has its limitations too in using a single-center approach with a limited sample size. Also, the occurrence of coughor other airway reflexes was not investigated. The dose of IV induction and inhalational agents for each patient was subjective. Measurement of plasma catecholamine levels, which is a more objective means of hemodynamic response, was not done because of laboratory restrictions. Measurement of time to recovery following extubation was not performed. Hence, multicentric, prospective studies with a larger sample size, accounting for coughing, anesthesia doses, catecholamine levels, and recovery time are encouraged to validate the results.

Conclusion

Addition of low-dose dexmedetomidine (0.25µg/kg) to the pregabalin and fentanyl premedication regimen is associated with greater blunting of HR and BP responses to airway instrumentation (laryngoscopy and intubation) in laparoscopic abdominal surgeries compared to pregabalin and fentanyl alone.

Conflict of interest: None.
Acknowledgments: None.
Funding source: None.

References

1. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G. Plasma catecholamine responses to tracheal intubation. Br JAnaesth 1983; 55:855-60.
2. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation.Br J Anaesth 1987; 59:295-9.
3. Perrin M, Fletcher A. Laparoscopic abdominal surgery. Continuing Education in Anesthesia. Critical Care & Pain 2004; 4:107-10.
4. Pohjavaara P, Telaranta T, Väisänen E. The role of the sympathetic nervous system in anxiety: Is it possible to relieve anxiety with endoscopic sympathetic block? Nord J Psychiatry 2003; 57:55-60.
5. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon the heart. Surg Gynecol Obstet 1940; 70:157-62.
6. Fox EJ, Sklar GS, Hill CH, Villanueva R, and King BD. Complications related to the pressorresponseto endotracheal intubation. Anesthesiology 1977; 47:524-5.
7. Bruder N, Ortega D, Granthil C. Consequences and prevention methods of hemodynamic changes during laryngoscopy and intratracheal intubation.Ann Fr Anesth Reanim 1992;11:57-71.

8. Stoelting RK, Hillier SC. Fentanyl- Pharmacology and physiology in anesthetic practice. In: Stoelting RK, Hillier SC, editors. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2012.
9. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia. 2004; 45:13-8.
10. De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 2001; 93:1205-9.
11. Ramsay MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J1974; 2:656-9.
12. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and peroperative fentanyl. Br J Anaesth 1992; 68:126-31.
13. Jaakola ML, Ali-Melkkilä T, Kanto J, Kallio A, Scheinin H, Scheinin M. Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. Br J Anaesth 1992; 68:570-5.
14. Lawrence CJ, De Lange S. Effects of a single preoperative dexmedetomidine dose on isoflurane requirements and peri-operativehemodynamic stability. Anesthesia 1997; 52:736-44.
15. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian JAnaesth 2011; 55:352-7.
16. Hazra R, Manjunatha SM, Manuar B, Basu R, Chakraborty S. Comparison of the effects of intravenously administered dexmedetomidine with clonidine on hemodynamic responses during laparoscopic cholecystectomy. Anaesth Pain & Intensive Care 2014; 18:25-30.
17. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 1992; 77:1134-42.
18. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology2000; 93:382-94.
19. Iyer V, Russell WJ. Induction using fentanyl to suppress the intubation response in the cardiac patient: what is the optimal dose? Anaesth Intensive Care 1988; 16:411-7.
20. Limn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 1979; 58:390-5.
21. Bajwa SJ, Kaur J, Singh A et al. Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian J Anaesth 2012; 56:123-8.

Table-1: Comparison of demographic and medical parameters between the two groups

Parameter	Subgroup	Group A		Group B	
		Count	Percentage (%)	Count	Percentage (%)
Gender	Male	8	26.67	8	26.67
	Female	22	73.33	22	73.33
Age (years)	20-29	15	50	15	50
	30-39	7	23.33	8	26.67
	40-49	6	20	3	10
	50-59	2	6.67	4	13.33
	Mean ± SD	33.07 ±10.61		32.16 ± 11.09	
BMI (kg/m^2)	14-19	3	10	1	3.33
	19-25	27	90	29	96.67
	Mean ± SD	21.92 ± 2.08		22.09 ± 1.93	
ASA status	ASA I	26	86.67	26	86.67
	ASA II	4	13.33	4	13.33
Intraoperative fentanyl requirement frequency	0	23	76.67	25	83.33
	1	3	10	3	10
	2	4	13.33	2	6.67
Postoperative analgesic requirement frequency	0	0	0	0	0
	1	14	46.67	25	83.33
	2	16	53.33	4	13.33
	3	0	0	1	3.33
Ramsay Sedation Score (before pre-medication)	RAMSAY 1	16	53.33	15	50
	RAMSAY 2	14	46.67	15	50
	RAMSAY 3	0	0	0	0
Ramsay Sedation Score (before intubation)	RAMSAY 1	0	0	0	0
	RAMSAY 2	30	100	30	100
	RAMSAY 3	0	0	0	0

ASA:American society of anesthesiologists; BMI: Body mass index

Figure-1 Visual Analogue Scale

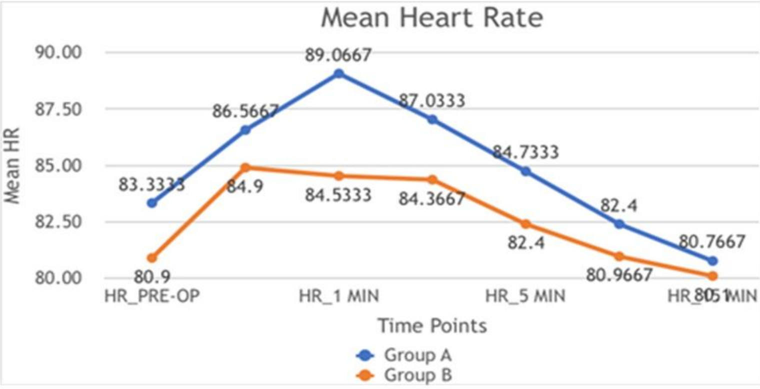

Figure 2 Change in the mean heart rate

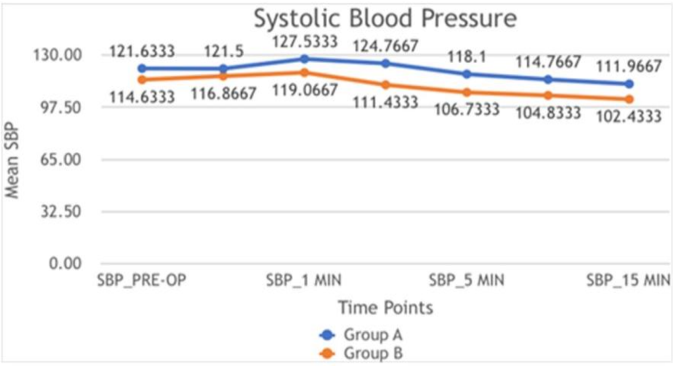

Figure 3 Change in the mean systolic blood pressure

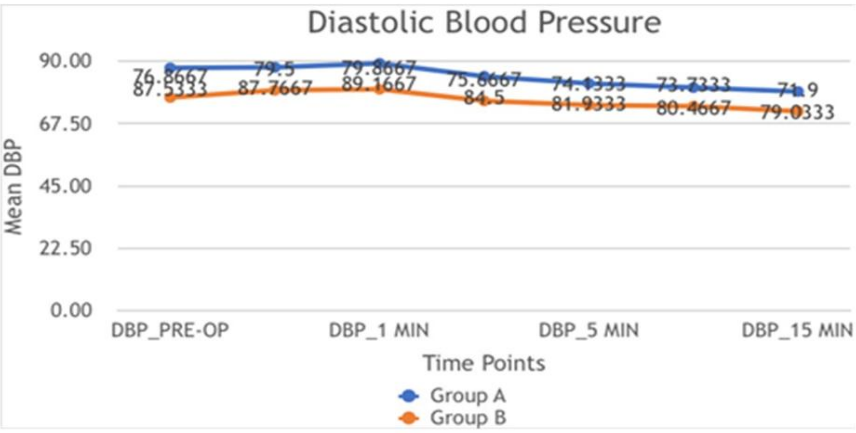

Figure 4 Change in the mean diastolic blood pressure

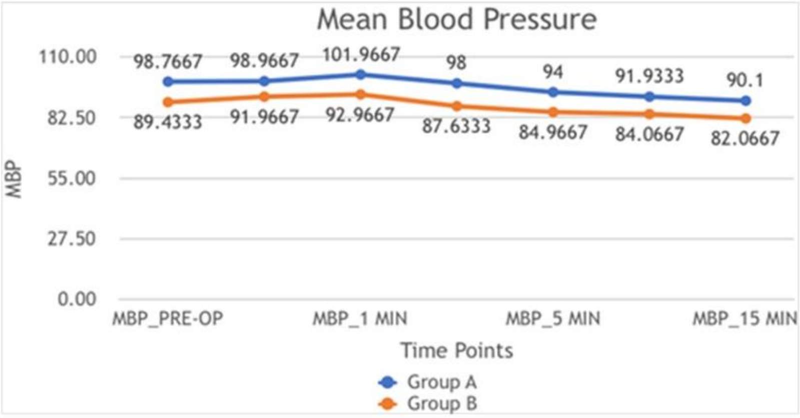

Figure 5 Change in the mean arterial pressure