

## ORIGINAL RESEARCH

## GENERAL ANESTHESIA

# Role of pre-extubation fentanyl in mastectomy: a randomized, controlled, double-blind study

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## Abstract

**Background:** Both tracheal intubation and extubation are associated with dangerous consequences such as tachycardia, hypertension, myocardial ischemia and arrhythmias. The aim was to evaluate pre-extubation two different doses of fentanyl on hemodynamic stabilization and delayed recovery in mastectomy.

**Methodology:** The randomized controlled double-blind study was conducted on 126 patients aged 16–60 years, with controlled hypertension, receiving chemotherapy before surgery and underwent mastectomy for breast cancer. Patients were randomly allocated into 3 equal groups. Before extubation, patients received 10 ml saline in group (C), 1 µg/kg fentanyl in Group-F1: and 2 µg/kg fentanyl in Group-F2. Mean arterial blood pressure (MAP) and heart rate (HR) were recorded at T1 (after maintenance of anesthesia), T2 (after giving the test drug), T3 (immediately after extubation), T4 (5 min. after extubation) and T5 (15 min after extubation).

**Results:** MAP was significantly lower in fentanyl groups compared to Group-C at T2 and T3 without significant deference between fentanyl groups. HR was significantly lower in fentanyl groups compared to Group-C and in Group-F2 compared to Group-F1 at T3, T4 and T5. Time of extubation was significantly prolonged in Group-F2 compared to Group-F1 and Group-C without a significant difference between Group-F1 and Group-C.

**Conclusions:** Pre-extubation fentanyl 1 µg/kg blunted cardiovascular responses to extubation without respiratory depression or prolonged recovery. Pre-extubation fentanyl 2 µg/kg provide more control in HR but with delay in the extubation time compared to 1 µg/kg of fentanyl.

**Key words:** Pre-Extubation, Fentanyl, Mastectomy, Hemodynamics, Recovery

**Preregistration:** The study was registered in the Ethical Committee of Faculty of Medicine, Cairo University, Cairo, Egypt (approval number: 281)

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**Abbreviations:** CST=Craniosacral therapy; SMT=Sensorimotor training; NCLBP=Nonspecific chronic low back pain; VAS=Visual analogue scale; ODI=Oswestry disability index, BDI-II=Beck depression inventory-II, and SF-36=Short Form-36; CSF=cerebral spinal fluid; CSS=craniosacral system; PRM=primary respiratory movements

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## 1. Introduction

Both tracheal intubation and extubation are associated with hazardous consequences such as tachycardia,

arrhythmias, myocardial ischemia, hypertension as well as elevation of intracranial and intra-abdominal pressure.<sup>1</sup> These potentially serious side effects during tracheal intubation can be solved and managed

effectively and rapidly by administration of inhalational or intravenous (IV) anesthesia.<sup>2</sup> On contrary, during extubation, if hypertensive crises occur especially in hypertensive patients, anesthesiologist, if aware by such problem, may have less weapons to manage it.<sup>3</sup> These hypertensive crises should pay more attention in patients with malignant tumors, as malignancy itself may induce abnormality in the proliferative pathway leading to increase peripheral resistance, as well as arterial hypertension which is the most frequent adverse effect of most chemotherapeutic agents (inhibitors of angiogenesis).<sup>4</sup> On a direct relation to the doses, these drugs can aggravate hypertension which pre-existing, or can lead to de novo hypertension to develop through dysfunction of the endothelial.<sup>5</sup>

Hypertension may occur at any time during chemotherapeutic treatment. Acute complications include proteinuria with renal thrombotic microangiopathy, heart failure, operative related hypertensive crisis and intracerebral hemorrhage.<sup>5</sup> Thus, it's very important to obtund the stress response of both intubation and extubation in cancer patients undergoing surgery with paying more attention to extubation hypertensive crises, especially in patients under chemotherapy.

Fentanyl, is a short acting opiate, has been used to attenuate stress response of both extubation and intubation. The peak effect on respiratory depression of a single IV dose of fentanyl citrate is noted between 5 to 15 min after injection. Several doses of fentanyl (0.5, 1, 2, 2.5 µg/kg) were used to obtund the stress during induction of anesthesia.<sup>6</sup> Also, fentanyl has been used to smoothen emergence from general anesthesia (GA) after surgery.<sup>7</sup> However, its use at the end of the surgery in adult hypotensive cancer patient is still not fully studied.

The aim of the work is to evaluate the benefits of pre-extubation administration of two different doses of fentanyl on hemodynamic stabilization versus delayed recovery as a side effect in controlled hypertensive females receiving preoperative chemotherapy and scheduled for mastectomy.

## 2. Methodology

The randomized controlled double-blind study was conducted on 126 patients aged 16–60 years, body mass index (BMI): 20–40, with controlled hypertension, receiving chemotherapy before surgery underwent mastectomy for breast cancer.

Exclusion criteria were patients with co morbidity affecting drug pharmacokinetics (e.g., liver failure, kidney failure), asthmatic patients and heavy smokers.

The patients were randomly allocated into 3 equal groups (42 patients in each). All patients received the test drug or the placebo at the end of surgery, before extubation. Group (C): patients received 10 ml saline (placebo) as a control group, Group-F1: patients received 1 µg/kg fentanyl in 10 ml saline and Group-F2: patients received 2 µg/kg fentanyl in 10ml saline.

Randomization was done by a computer-generated list that was kept in a sealed envelope. Both patients and data collector were blinded to grouping.

### Interventions:

After the approval of the ethical committee and taking the patient's written informed consent, all patients in study groups received 2 mg midazolam IV as premedication, 30 min before induction of anesthesia. Monitoring included the standard monitors, namely ECG, body temperature, EtCO<sub>2</sub> and oxygen saturation and hemodynamic monitoring.

General anesthesia was induced by IV administration of 1.5 µg/kg fentanyl and 2 mg/kg propofol. Intubation was facilitated by IV administration of 0.5 mg/kg atracurium. 1 MAC isoflurane in 100% oxygen was used to maintain anesthesia. Muscle relaxation was achieved by IV administration of 0.1 mg/kg atracurium every 30 min guided by the application of nerve stimulator all through the operation till the time of extubation. Ventilation was controlled aiming to keep end tidal CO<sub>2</sub> in the range of 30–35 mmHg. All patients received 1gm paracetamol and 75 mg IM diclofenac sodium as multimodal intraoperative analgesia.

At the time of end of surgery (end of the surgical sutures), the inhaled anesthetic was discontinued, nasopharyngeal airway was placed before administering the reversal of the muscle relaxant. The patients included in the study were randomly allocated to receive either IV saline (Group-C), IV fentanyl 1 µg/kg (in Group-F1) or IV fentanyl 2 µg/kg (in Group F2) immediately before extubation. Then reversal of the muscle relaxant was done by neostigmine 0.05 mg/kg IV and atropine 0.01–0.02 mg/kg IV. The patients were allowed to inhale 100% oxygen before suction and tracheal extubation. Extubation was performed after achievement of: normal-ventilation, wakefulness, alertness, following commands, and the regain of gag or cough reflexes.

To control dramatic increase of blood pressure (20% above patient baseline) during or after extubation, patients were administered rescue drugs (e.g. lidocaine 1–1.5 mg/kg slowly IV bolus over 2–3 min or nitroglycerin IV infusion 5 µg/min increased by 5 µg/min every 3–5 min if required, up to 20 µg/min).

The duration of anesthesia (defined as the time from induction of anesthesia till the time of extubation) and time of extubation [defined as the time from the reversal of muscle relaxant and giving fentanyl till complete recovery (which was defined as achievement of normal-ventilation, awake, alert, follow commands, regain of gag or cough reflex) and extubation] were recorded.

Mean arterial blood pressure (MAP) and heart rate (HR) were recorded at T1 (Base line value): after maintenance of anesthesia. T2: after giving the test drugs, immediately before extubation. T3: Immediately after extubation. T4: 5 min. after extubation. T5: 15 min after extubation. Complication after extubation [desaturation ( $\text{SaO}_2 < 95\%$ ),

vomiting, coughing, laryngospasm and shivering] were recorded.

The primary outcome was MAP elevation (defined as an increase by 15% above the patient's baseline value). The secondary outcomes were HR, time of extubation and complications.

#### Statistical analysis:

The calculation of sample size was done by G\*. power 3.1.9.2 based on: 0.05  $\alpha$  error and 80% power of the study and expected primary outcome (incidence of MAP elevation) is 20–50%. Three cases were added to each group to overcome dropout; therefore, we recruited 42 patients in each group.

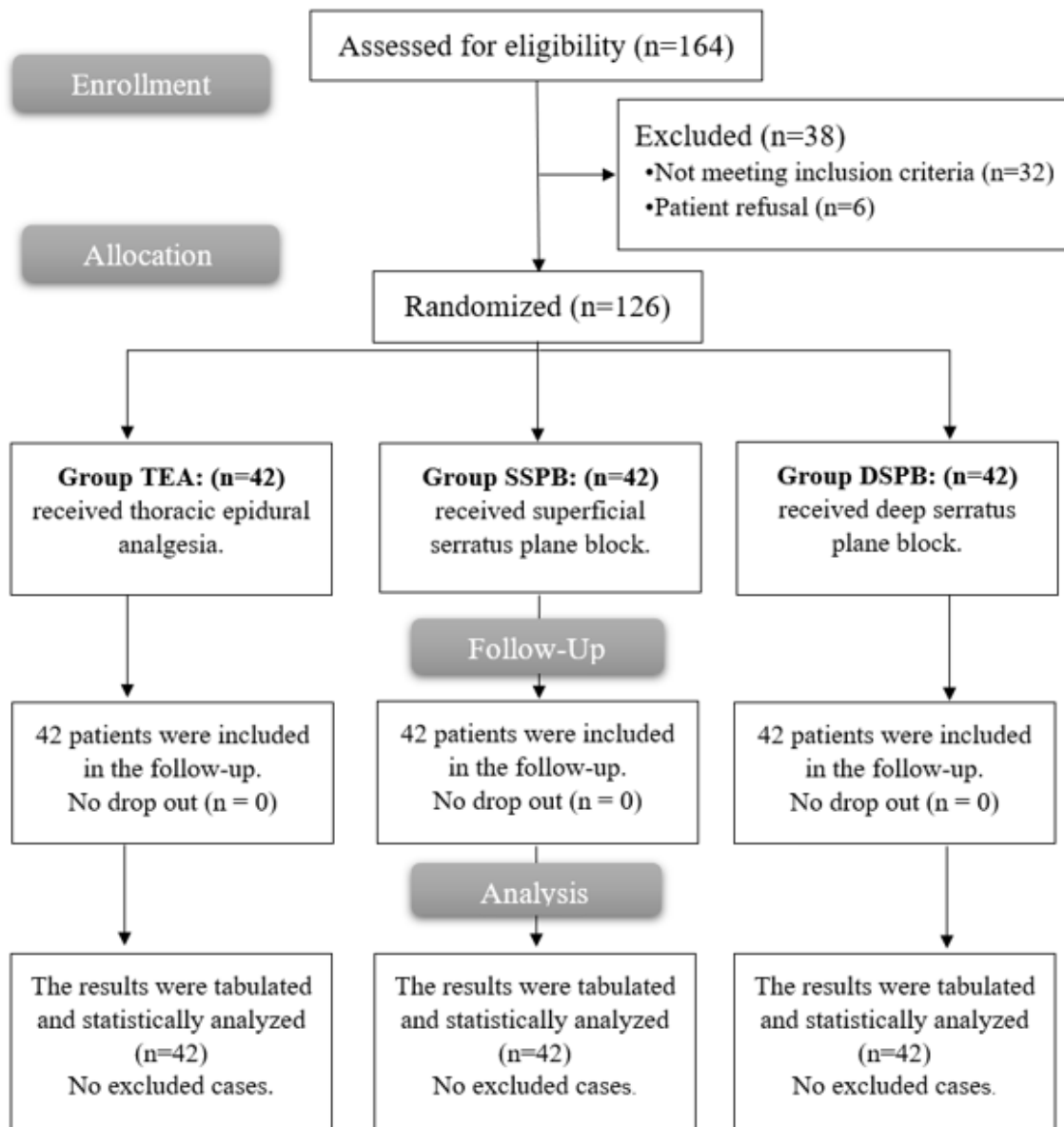


Figure 1: CONSORT flowchart of patients in the three groups

**Table 1: Demographic data of the three groups**

Parameters	Group-C (n=42)	Group-F1 (n=42)	Group-F2 (n=42)	P-value
Age (y)	42.64 ± 12.7	45.32 ± 10.4	44.3 ± 11.4	0.87
Weight (kg)	78.75 ± 12.7	81.5 ± 11.5	77.58 ± 10	0.252
Duration of surgery (min)	93 (57–130)	115 (90–157)	106 (55–131)	0.134

Data are present as mean ± SD or median (IQR)

**Table 2: Comparative complications in the groups**

Complications	Group-C (n=42)	Group-F1 (n=42)	Group-F2 (n=42)	p-value
Desaturation	1	2	2	0.8
Vomiting	2	4	3	0.69
Laryngospasm	0	1	0	0.3
Coughing	2	1	1	0.78
Shivering	4	3	2	0.69

Data are expressed as frequency.

Data was analyzed using SPSS v 17 (IBM©, Chicago, IL, USA). Qualitative data were presented as number and percent and were compared using Chi-square test. Quantitative parametric data were described as mean and standard deviation (SD) as appropriate. One way ANOVA test was used to compare data in studied groups with a Tukey Post Hoc test was performed to identify the level of significance. Quantitative parametric data were described as median and interquartile range (IQR) and were compared by Kruskal Wallis test. A two tailed  $p < 0.05$  was considered statistically significant.

### 3. Results

Flowchart of the patients in the three groups is shown in **Error! Reference source not found.**

Demographic data including age, weight and duration of surgery were insignificantly different among the three groups (**Error! Reference source not found.**).

MAP was significantly lower in fentanyl groups (F1, F2) compared to Group-C at T2 and T3 but without significant deference between the two doses of fentanyl. This means that fentanyl provides stability in between the readings of MAP from (T1) to (T5) without fluctuations as in the control group (**Error! Reference source not found.**). The incidence of MAP elevation was 54.8% in Group-C, 7.1% in Group-F1 and 2.4% in Group-F2 ( $p < 0.001$ ).

HR was significantly lower in fentanyl groups (F1, F2) compared to Group-C and in Group-F2 compared to Group-F1 at T3, T4 and T5. This meant than fentanyl 2 µg/kg (F2) was superior to the other groups in HR stabilization, so this is of great benefit for cardiac and ischemic patients and that fentanyl provides stability in between the readings of the HR from (T1) to (T5) without fluctuations as in the control group (**Error! Reference source not found.**).

Time of extubation was significantly prolonged in Group-F2 compared to Group-F1 and Group-C without a significant difference between Group-F1 and Group-C. This means that fentanyl 2 µg/kg delayed time of extubation compared to 1 µg/kg or control (**Error! Reference source not found.**).

There were no significant differences between the three groups regarding complications, e.g., desaturation, vomiting, coughing, laryngeal spasm and shivering (**Error! Reference source not found.**).

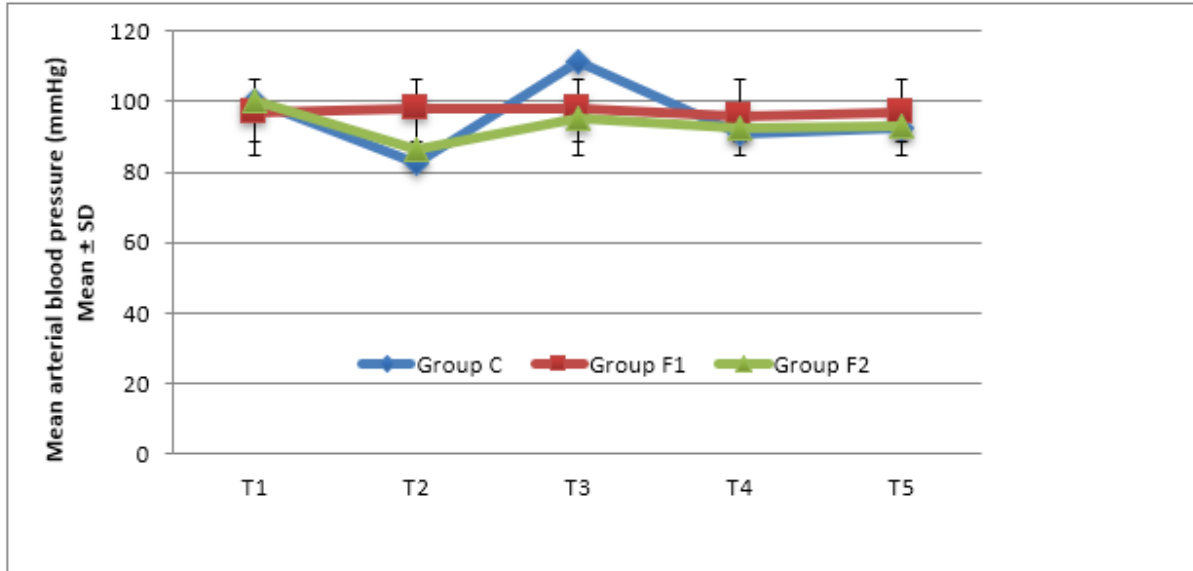
### 4. Discussion

Tracheal extubation may provoke stressful responses and may irritate the airway leading to straining and coughing. Thus MAP and HR will be elevated during emergence and extubation and can trigger a hazardous increase in the myocardial oxygen demand in patients with coronary artery disease (CAD) and those with risk factors for CAD.<sup>8</sup>

Many drugs are used to attenuate the extubation response e.g., short-acting opioids, esmolol, labetalol, lidocaine IV, and intratracheal instillation of local anesthetic solution. A dependable method for smooth and rapid extubation is still not fully evolved.<sup>9</sup>

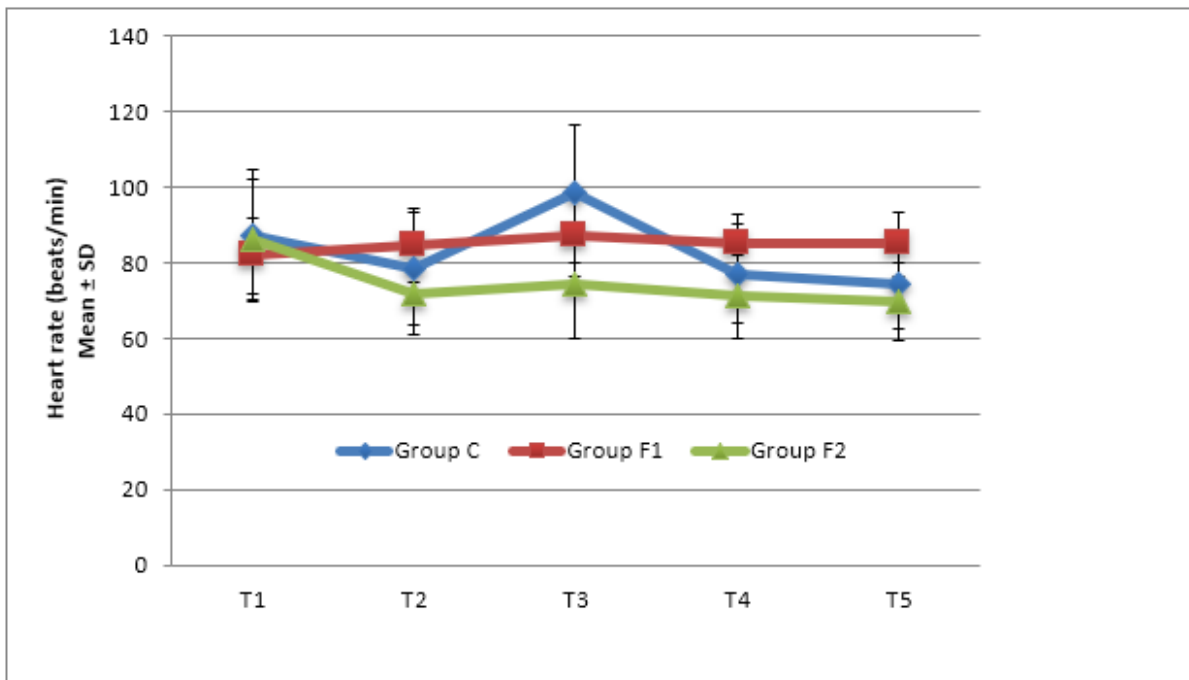
Fentanyl has been used to blunt the hemodynamic changes related to laryngoscopy and intubation.<sup>10</sup>

The rationale for using fentanyl at 1 or 2 µg/kg in our trial was as follows: (i) During general inhalational



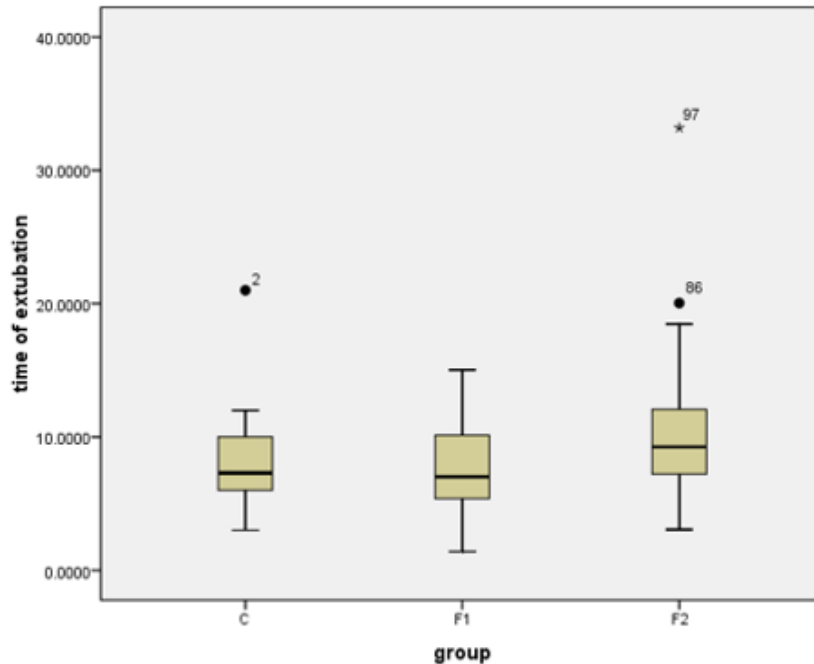
**Figure 2: Mean arterial blood pressure in the three groups**

T1 (after maintenance of anesthesia), T2 (after giving the test drugs), T3 (Immediately after extubation), T4 (5 min. after extubation), T5 (15 min after extubation)



**Figure 3: Heart rate in the three groups**

T1 (after maintenance of anesthesia), T2 (after giving the test drugs), T3 (Immediately after extubation), T4 (5 min. after extubation), T5 (15 min after extubation)



**Figure 4: Time of extubation (min) in the three groups**

The middle solid black line is median, the upper and lower margins are IQR (interquartile range), and whiskers are minimum & maximum

anesthesia, fentanyl 1–2  $\mu\text{g}/\text{kg}$  IV was used as a supplement; (ii) In an effort to minimize sudden circulatory alterations in response to numerous surgical stimuli, fentanyl 2–10  $\mu\text{g}/\text{kg}$  IV was used; and (iii) The usage of low-dose fentanyl to reduce cardiovascular compromise after intubation has been suggested in many trials.<sup>11</sup>

The suppressive effects of fentanyl on tachycardia can explain the rationale of its use in this setting, since HR is the key controllable determinant of myocardial oxygen balance. In patients with CAD, fentanyl can thus be successfully used to attenuate the cardiovascular responses to extubation.<sup>12</sup>

We studied patients with controlled hypertension, on chemotherapy for breast cancer. This population was chosen for their higher risk of cardiovascular complications.<sup>13</sup> In our study, both fentanyl groups showed a lower MAP and HR compared to the control group. More control of HR was with fentanyl 2  $\mu\text{g}/\text{kg}$  but with prolongation in the recovery time compared to other groups. There were no significant complications related to fentanyl use.

Our results were in agreement with a study by Lemma et al.<sup>14</sup> who showed that administration of fentanyl 1  $\mu\text{g}/\text{kg}$  IV, 10 min before the end of surgery, attenuated hemodynamic response to extubation in ear, nose and throat surgeries. Younes et al.<sup>15</sup> demonstrated that fentanyl 2  $\mu\text{g}/\text{kg}$  decreased HR and MAP significantly and showed a greater degree of sedation without any

deleterious effects. Rani et al. was also in line with our results as they showed that the use of fentanyl 1  $\mu\text{g}/\text{kg}$  before extubation decreased HR and MAP significantly.<sup>9</sup>

Also our results were supported by a study made by Nho et al. to evaluate the role of remifentanyl infusion on recovery profile such as coughing and cardiovascular responses after GA in endoscopic sinus surgery under GA using total IV anesthesia (propofol and remifentanyl).<sup>16</sup> At the end of the surgery, propofol was ceased and the infusion of remifentanyl was stopped in the control group and maintained in the remifentanyl group at a target organ concentration of 1.5 ng/ml until extubation. There was no significant difference in time to extubation. Increases in HR and MAP occurred during emergence in the control group compared with baseline values. Increases in HR were attenuated in the remifentanyl group and MAP decreased during recovery compared with baseline values. Moderate or severe coughing was observed only in the control group with a significant difference.

In the study by Nishina et al.<sup>7</sup> patients were randomly assigned to three group, and fentanyl (1 or 2  $\mu\text{g}/\text{kg}$ ), or saline (as a control) was given at the time of peritoneal closure in elective gynecological surgery. The HR and MAP increased significantly during extubation in the control group. Fentanyl 2  $\mu\text{g}/\text{kg}$  attenuated the increases in these variables more effectively than fentanyl 1  $\mu\text{g}/\text{kg}$  without prolonging the recovery.



Postoperative somnolence and respiratory depression were not observed. The time interval from the study drug to extubation was similar in each group. This difference may be due to the difference in drugs used in anesthesia and earlier fentanyl administration (time of peritoneal closure) but in our study (time of discontinuation of anesthesia).

## 5. Conclusion

In controlled hypertensive female patients, on chemotherapy scheduled for mastectomy for breast cancer; pre extubation fentanyl 1 µg/kg IV is a simple, practical and effective method in obliterating hemodynamic responses to extubation. This dose does not lead to prolonged extubation time or respiratory depression. Fentanyl 2 µg/kg provides better control of the HR than 1 µg/kg which may be of great benefit for the patients with CAD but with delay in the extubation time when compared to 1 µg/kg of fentanyl.

## 6. Conflicts of Interest

Nil

## 7. Author Contributions

All authors contributed to the paper.

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