

Research Article

Comparison between oral pregabalin and intravenous fentanyl on attenuation of blood glucose level as one modality of stress response to tracheal intubation and decreasing early post operative pain

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Abstract

Introduction: Endotracheal tube remains the gold standard airway device for securing the airway during general anesthesia. However, Laryngoscopy and tracheal intubation are associated with haemodynamic stress responses due to sympathetic stimulation, which results in marked increase in heart rate, blood pressure, circulating catecholamines. **Aim of the work:** To evaluate the effect of oral pregabalin and intravenous fentanyl on attenuation of blood glucose level as one modality of the stress response to tracheal intubation and decrease early postoperative pain in elective upper abdominal surgeries. **Patients and Methods:** The study included seventy five (75) patients, aged 18-40 years old of both sex, ASA I or II, undergoing elective upper abdominal surgeries open cholecystectomy, renal stone ,pyeloplasty and nephrectomy under general anaesthesia with endotracheal intubation. The patients were randomly divided into one of three groups, of 25 patients each (using computer generated randomization list): *Group (I): received 2µg/kg fentanyl iv route , 5 minutes before surgery.*Group (II): received 150 mg pregabalin oral route two hours before surgery.*Group (III): Received 150 mg pregabalin oral 2 hours before surgery and 2µg/kg fentanyl 5 minutes before surgery. **Results:** As regard MAP, HR, RR were significant lower in both groups [I] & [III] when compared to group [II] and signifacntly lower in group [I] when compared to group [III]. Although there was Statistically significant reduction in values of MAP and HR in varying degrees when compared with their baseline values, there was no clinically symptomatic hypotension, bradycardia or respiratory depression required any treatment with naloxone or supplemental oxygen. **Discussion:** laryngoscopy alone or with tracheal intubation increases the arterial blood pressure and catecholamine levels, while intubation significantly increases heart rate This can also lead to increased risk of myocardial ischemia during tracheal intubation.**We recommend:** using fentanyl (2µg/kg) intravenous 5 minutes and oral pregabalin (150 mg) 2 hours before operation for controlling of hemodynamic stress response and post operative analgesia also on attenuation of blood glucose level as one modality of stress response in patients undergoing upper abdominal surgeries under general anaesthesia

KeyWords: **ASA:** American society of anaesthesiology, **Hr:** Hour, **BP:** blood pressue, **ET:** endotracheal.

Introduction

In 1940, Reid and Brace first described haemodynamic response to laryngoscopy and intubation. As it lead to an average increase in blood pressure by 40-50%, 20% increase in heart rate, the hormonal effect of tracheal intubation is elevation of both epinephrine and norepinephrine levels, and subsequent increase of blood glucose level which occurs in patients undergoing

surgeries in non diabetic patient, its degree related to the degree of stress response (Shribman, Smith et al., 1987).

The increase in blood pressure and heart rate is usually transient and variable, the effects usually occur within thirty seconds to at least less than ten minutes. Wide variety of pharmacological agents in combination with primary anaesthetic were used to

attenuate the haemodynamic response to laryngoscopy and endotracheal intubation like lignocaine (Gulabani, Gurha et al., 2015), alfentanil, remifentanil (Entezariasl, Akhavanakbari et al., 2012), nifedipine, beta-blockers, clonidine, magnesium sulfate, with varying results. All of them require time for preparation and administration, Hence, the search for an ideal agent to attenuate the haemodynamic responses is still continuing.

Preemptive analgesia is analgesic administration that precedes the painful stimulus, thus improving postoperative pain control. It is an antinociceptive treatment that prevents the establishment of altered processing of afferent input, which amplifies postoperative pain. This technique is utilized in acute postsurgical pain management to improve the efficacy of analgesics and thereby reduce the requirement for opioids (Clark et al., 2014).

Pregabalin is an γ -aminobutyric acid analog that binds to the $\alpha 2$ - δ subunit of presynaptic voltage-gated calcium channels, It reduces the depolarization-induced calcium influx at nerve terminals, with a consequent reduction in the release of several excitatory neurotransmitters, including glutamate, noradrenaline, substance P, and gastrin-releasing peptide (Anand et al., 2017).

The administration of oral pregabalin preoperatively has been reported to reduce acute postoperative pain and to prolong the duration of anesthesia produced by single-injection peripheral nerve block (Agarwal et al., 2008).

Fentanyl is a potent narcotic, analgesic used to decrease haemodynamic response to tracheal intubation, postoperative pain and preemptive analgesia. Fentanyl is a strong, synthetic (man-made) narcotic that is similar to morphine. Fentanyl stimulates receptors on nerves in the brain to increase the threshold to pain (the amount of stimulation it takes to feel pain) and reduce the perception of pain (the perceived importance of the pain) (Ettienne et al., 2017).

Fentanyl is available in transdermal (for application to the skin), transmucosal (for application to mucus membranes) and parenteral (injectable) forms (Higashikawa et al., 2008).

Aim of the work

To evaluate the effect of oral pregabalin and intravenous fentanyl on attenuation of blood glucose level as one modality of the stress response to tracheal intubation and decrease early postoperative pain in elective upper abdominal surgeries.

Patients and Methods

The study included seventy five (75) patients, aged 18-40 years old of both sex, ASA physical status I or II, undergoing elective upper abdominal surgeries open cholecystectomy, renal stone, pyeloplasty and nephrectomy under general anaesthesia with endotracheal intubation.

Pre-operative assessment and preparation

All patients were assessed clinically after taking medical history and through physical examination and investigated for exclusion of the above mentioned contraindications, laboratory work needed was complete blood picture (CBC), Prothrombin time and concentration, liver function, renal function and resting ECG was done.

The patients were randomly divided into one of three groups, of 25 patients each (using computer generated randomization list):

***Group (I):** received 2 μ g/kg fentanyl iv route, 5 minutes before surgery.

***Group (II):** received 150 mg pregabalin oral route two hours before surgery.

***Group (III):** Received 150 mg pregabalin oral 2 hours before surgery and 2 μ g/kg fentanyl 5 minutes before surgery.

Technique of the study:

On arrival to the operating room a peripheral intravenous line was inserted and standard monitors were attached (non invasive blood pressure, pulse oximetry and 5 leads ECG).

The patients were pre oxygenated for 3 minutes. Following pre oxygenation, anaesthesia was induced with propofol 2.5-3.5mg/kg till loss of verbal contact and atracurium 0.5mg/kg IV, ventilation was done by face mask for 3 minutes.

Laryngoscopy and intubation were performed by an experienced anaesthesiologist using an appropriate sized Macintosh blade and low pressure cuffed endotracheal tube.

Anaesthesia was maintained using isoflurane 1MAC, after completion of surgical procedure and patients recovery after cessation of inhalational anaesthesia by giving atropine in adose (0.01-0.02mg /kg) and neostigmine at a dose (0.05mg/kg) and extubation, patients referred to PACU.

Hemodynamics: heart rate (HR), blood pressure (BP) and oxygen saturation pre-operative after induction after intubation and every 5 minutes till the end of operation.

Postoperative pain was controlled by rescue analgesics (15 mg/kg/dose paracetamol) and if pain continuo if VAPS more than 3 we will add another analgesia nalbuphine (0.2-0.5mg/kg). post operative pain was assessed by the patient using the

visual analog pain scale (VAPS, 0=no pain; 10=worst possible pain) immediate post operative, every 2 hours till 14 hours after operation. The time of first request for postoperative analgesia and the number of analgesia were recorded.

Blood glucose level is assessed prior to induction, before intubation and 5 minutes after extubation.

Measured parameters:

***Hemodynamic parameter**ts: (heart rate, systolic, diastolic and mean arterial blood pressure and oxygen saturation were recorded preoperative, after induction, after intubation and every 5 minutes till the end of operation and 6 hours after operation.

***Post operative pain** was assessed by using the visual analogue pain scale, analgesic requirement and time of first analgesic request.

***Blood glucose level** is assessed prior to induction, before intubation and 5 minutes after extubation.

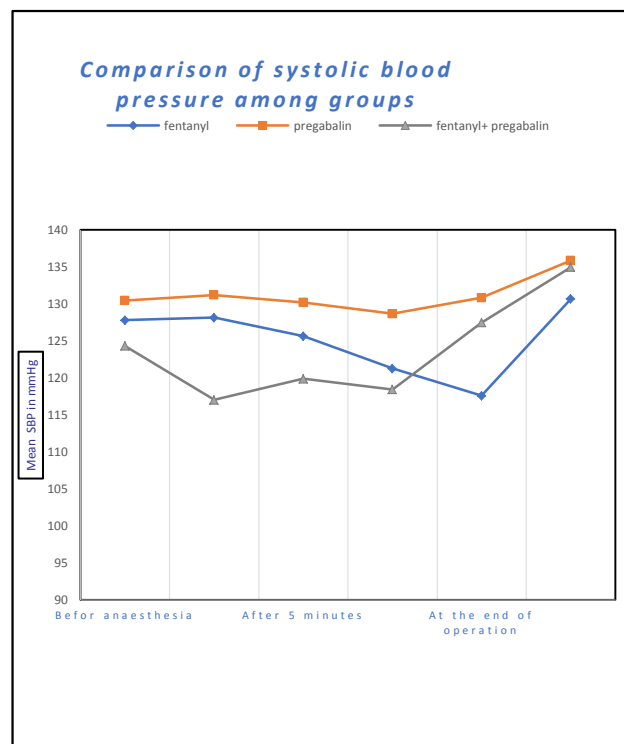
***Incidence of any of the following possible complications** during first 24 hours post-operative was recorded: drowsiness, dizziness, dry mouth and nausea, vomiting and heachade

Results

Table (1): Patient's characteristics.

| Variables | Fentanyl Group N=25 | Pregabalin Group N=25 | Fentanyl + pregabalin Group N=25 | P-value |
|---|------------------------|--------------------------|-------------------------------------|---------|
| Age in years Mean \pm SD | 34.6 \pm 7.7 | 41.2 \pm 7.7 | 32.9 \pm 14.9 | NS |
| Sex: n (%) | | | | NS |
| Males | 12(48%) | 16(64%) | 16(64%) | |
| Females | 13(52%) | 9(36%) | 9(36%) | |
| ASA: n (%) | | | | NS |
| Grade I | 23(92%) | 19(76%) | 20(80%) | |
| Grade II | 2(8%) | 6(24%) | 5(20%) | |
| Weight in kg Mean \pm SD | 70.6 \pm 8.09 | 70.4 \pm 7.05 | 67.2 \pm 7.4 | NS |
| Type of operation: n (%) | | | | NS |
| Open cholecystectomy | 3(12%) | 2(8%) | 2(8%) | |
| Stone kidney | 13(52%) | 15(60%) | 16(64%) | |
| Nephrectomy | 4(16%) | 5(20%) | 4(16%) | |
| Pyeloplasty | 5(20%) | 3(12%) | 3(12%) | |
| Duration of surgery in hours Mean \pm SD | 1.88 \pm 0.21 | 1.85 \pm 0.22 | 1.74 \pm 0.25 | NS |

The 3 groups were comparable with respect to age, gender, weight, ASA grade, type of surgery, duration of laryngoscopy and duration of surgery. There were no statistical significant difference (p-value >0.05) between three groups.



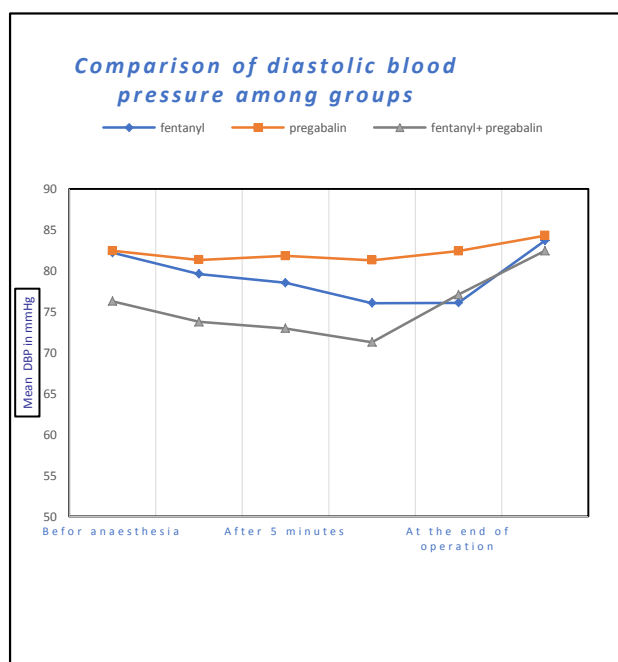
Hemodynamics among groups, Heart rate, systolic, diastolic and mean arterial blood pressure preoperatively showed insignificant difference between three groups.

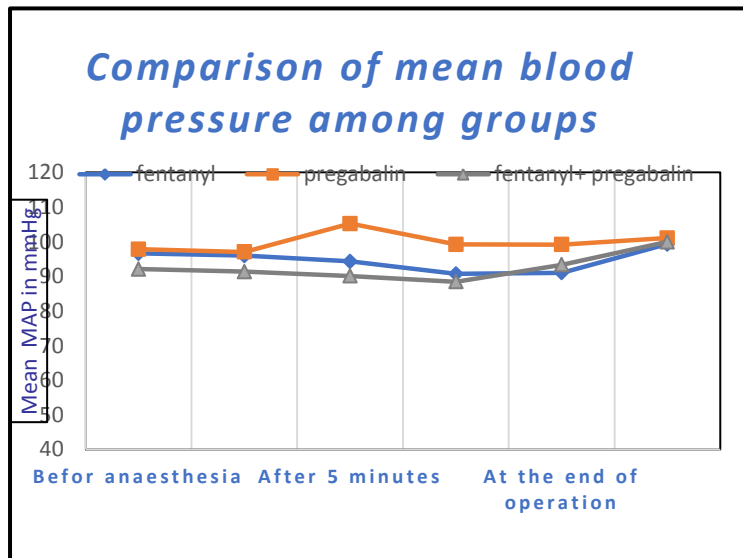
After induction of anaesthesia there was significant difference between group [I] fentanyl and group [III] both and between group [II] pregabalin and group [III] both as there was significant difference in hemodynamics in group [III].

After 5 min and 10 min of intubation there was significant difference between group [I] fentanyl and group [II] pregabalin and also between group [II] pregabalin and group [III] both as there was significant increase in HR, SBP, DBP and MABP in pregabalin group after 5 min and 10 min after the end of operation and after 6 hours post operative there was insignificant difference between the three groups.

heart rate (beat/min) among studied groups.

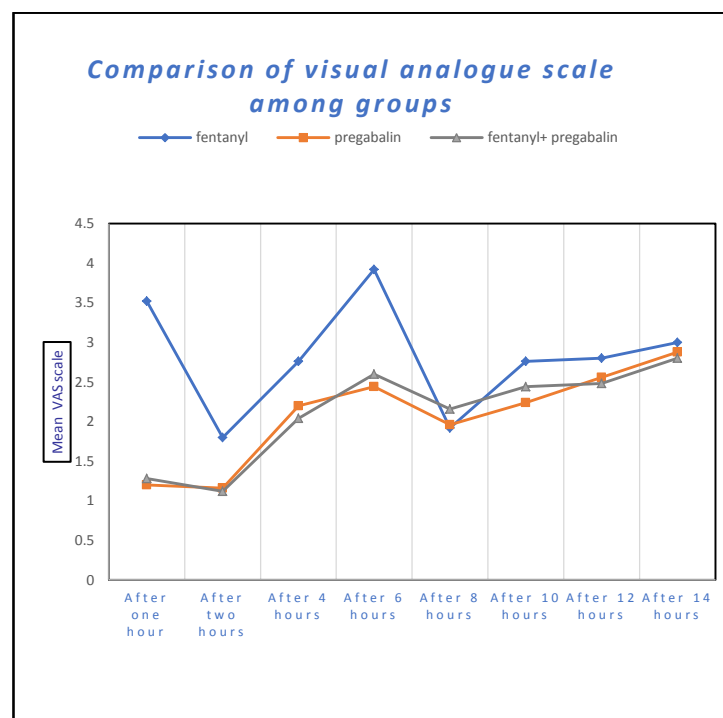
| Times | Fentanyl Group N=25 | Pregabalin Group N=25 | Fentanyl + pregabalin Group N=25 | | P-value | | |
|---------------------------------------|------------------------|--------------------------|-------------------------------------|------------------|--------------------|-----------------|----------------|
| | Mean ±SD | Mean ±SD | Mean ±SD | Between 3 groups | fentanyl & pregaba | fentanyl & both | pregaba & both |
| Befor anaesthesia | 93.88±12.8 | 89.80±8.9 | 89.88±5.7 | 0.060 | 0.137 | 0.111 | 0.074 |
| After induction of anaesthesia | 94.76±9.8 | 92.36±8.9 | 85.64±9.04 | 0.003** | 0.346 | 0.001** | 0.013* |
| 5 minutes after intubation | 94.76±7.5 | 99.76±9.5### | 88.54±9.6 | 0.010* | 0.043* | 0.051 | 0.008** |
| 10 minutes after intubation | 89.76±8.9 | 97.20±9.9## | 85.52±6.5 | 0.012* | 0.009** | 0.060 | 0.008** |
| At the end of operation | 88.52±10.8# | 89.40±6.5 | 84.64±12.3 | 0.074 | 0.066 | 0.976 | 0.050 |
| After 6 hours from operation | 91.40±10.7 | 92.92±5.2 | 91.64±11.6 | 0.836 | 0.579 | 0.930 | 0.640 |





As regard **Visual analogue pain scale** by comparing (VAPS) of the three groups post operative after 1hr, 2hrs, 4hrs, 6hrs, 8hrs, 10hrs, 12hrs and 14hours revealed that there was significant difference between

fentanyl group [I] and pregabalin group [II] also between fentanyl group [I] and both group [III] fentanyl and pregabalin after 1hr, 2hrs and after 4hours post operative



Discussion

In our study (75) male and female patients aged from 18-60 years old from ASA class I or II undergoing elective upper abdominal surgeries stone kidney, pyeloplasty, nephrectomy and open cholecystectomy under

general anesthesia randomly divided into three equal groups (25) in each group. Anesthetic technique was standardized in all the groups, group (I) patient received (2µg/ kg) iv fentanyl 5min before induction of anesthesia, group (II) patient received

(150 mg) oral pregabalin before operation for about 2 hours, group (III) patient received (2 μ g/kg) iv fentanyl 5 min before operation, (150mg) oral pregabalin 2 hours pre operative.

In the current study we found that using preoperative intravenous fentanyl is effective on attenuation of haemodynamic response to tracheal intubation with limited effect on postoperative analgesia, also we found that preoperative oral pregabalin is an effective method for post operative analgesia with mild effect on attenuation of haemodynamic response as compared to fentanyl, after upper abdominal surgeries resulted in longer duration of analgesia, lesser analgesic consumption postoperative with minimal side effect.

In our research we found that intravenous fentanyl was effective in attenuating the hypertensive response to ET intubation. SBP, DBP, and MAP values did not increase significantly after intubation in group (I) patients received iv fentanyl and group (III) patients received both iv fentanyl and oral pregabalin. Although group (II) patients received oral pregabalin showed significant rise of SBP, DBP, and MAP after intubation, compared to baseline readings. Also fentanyl was effective in attenuation of tachycardia to ET intubation. HR did not increase significantly after intubation in group (I) patients received iv fentanyl and group (III) patients received both iv fentanyl and oral pregabalin as compared to group (II) patients received oral pregabalin. Fentanyl also is effective on attenuation of blood glucose level which considered one modality of stress response fentanyl keep blood glucose level within its normal values in most patients in our study without any attacks of hyper or hypoglycemia.

Several studies evaluated the efficacy of fentanyl and pregabalin to obtund the hemodynamic response to endotracheal intubation.

(Kumar, Seth et al., 2016) used fentanyl, lignocaine nebulization, and a combination of both on attenuation of the hemodynamic response to laryngoscopy and tracheal intubation. They concluded that, IV

fentanyl 2 μ g/kg administered 5 min before induction was found to be the most effective in attenuating the hemodynamic response. It is a part of the routine anesthesia regimen and was found to be a safe and effective method in attenuating the hemodynamic response to laryngoscopy and intubation this is in agreement with our results.

(Hoda & Khan, 2011) Hoda and Khan, (S. Parida, N. C. Ashraf et al., 2015) Parida et al., Mireskandari et al., (Pouraghaei, Moharamzadeh et al., 2014), Malde and Sarode also found IV fentanyl effective in blunting hemodynamic response to endotracheal intubation.

(A Malde et al., 2006) used Fentanyl Versus Lignocaine on attenuation of the hemodynamic response to endotracheal Intubation: they concluded that given 5 minutes prior to intubation, lignocaine (1.5 mg/kg) and fentanyl (2 μ g/kg) both attenuated the rise in pulse rate, though fentanyl was better. Lignocaine attenuated the rise in blood pressure with intubation whereas fentanyl prevented it totally.

In agreement with our study, Ko et al., designed a study to examine the optimal time of injection of fentanyl. Patients received fentanyl (2 μ g/kg) 1, 3, 5, or 10 min before tracheal intubation. They concluded that the most effective time to administer fentanyl to protect circulatory responses to laryngoscopy and tracheal intubation is 5min before tracheal intubation. Fentanyl is often used to reduce the hemodynamic response to tracheal intubation. Administration of fentanyl at the optimal time reduces the dose required. Therefore, we selected fentanyl dose of 2 μ g/kg given 5 minutes prior to intubation like our study (Ko, Kim et al., 1998).

Another study in agreement with our study, Adachi et al., used 2 μ g/kg fentanyl just before induction in order to prevent cardiovascular stress. They found that fentanyl was more effective in prevention of cardiovascular hemodynamic response secondary to endotracheal intubation than prevention of hemodynamic response to laryngoscopy. They reported that this

effect of fentanyl was related with the interaction with plasma concentrations of the anesthetics that were used for induction (Adachi, Satomoto et al., 2002) .

On the other hand, Hussain et al., compared the effects of 2 µg/kg fentanyl and 2 mg/kg esmolol that were administered 2 min before laryngoscopy and intubation and reported that fentanyl was inadequate to prevent the increases in heart rate and blood pressure. They also showed that esmolol prevented the increase in heart rate.

In this study, they found that 2 mg/kg esmolol decreased systolic, diastolic and mean arterial pressures more than 2 µg/kg fentanyl, but there was not any difference between two groups according to prevention of the increase in heart rate (Hussain & Sultan, 2005) requirement) higher patient satisfaction score when compared with using every drug alone or placebo respectively in patients who underwent spine fixation surgery.

Conclusion

Through this study, we concluded that:

Preoperative intravenous fentanyl 2µg/kg as well as oral pregabalin 150 mg is effective in attenuation of hemodynamic stress response to laryngoscopy and tracheal intubation. Fentanyl was found to be more effective than pregabalin in lowering of blood pressure and heart rate changes associated with laryngoscopy and tracheal intubation and blood glucose level as one modality of stress response. Pregabalin gives better postoperative analgesia, as compared to fentanyl.

Group (III) fentanyl and pregabalin was the best of all as regarding attenuation of haemodynamic response to laryngoscopy and decreasing early post operative pain also are effective on attenuation of blood glucose level as one modality of stress response. .

Recommendation

We recommended using fentanyl (2µg/kg) intravenous 5 minutes and oral pregabalin (150 mg) 2 hours before operation for controlling of hemodynamic stress response and post operative analgesia also on

attenuation of blood glucose level as one modality of stress response in patients undergoing upper abdominal surgeries under general anaesthesia.

Further studies are still needed to establish the efficacy and safety of these drugs in patients with co-morbid conditions and in patients of extreme age group and avoiding narcotic policy in anaesthesia to coapt with general condition of co-morbid patients, COPD, patients with Asthma, Narcotic allergy and Addiction.

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