Comparative Effects of Fentanyl, Medazolam, Lignocaine and Propranolol on Controlling the Hemodynamic Pressor Response during Laryngoscopy and Intubation

May S. Al-Sabbagh*,[1]
*Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Laryngoscopy and tracheal intubation are considered the most invasive stimuli in anesthesia. They provoked cardiovascular responses that include hypertension, tachycardia and dysrhythmias. Various pharmacological approaches have been used to blunt or attenuate such pressor responses. The present study was designed to evaluate the effect of medazolom, lignocaine and propranolol as a valuable adjuvant to fentanyl in attenuating hemodynamic responses to endotracheal intubation in normotensive patients. Thirty two patient with physical status I or II according to the score of American Society of Anesthesiologist (ASA), scheduled for elective surgery under standard general anesthesia, were randomly allocated into four groups (8 patients in each group), assigned as F, M, L and P groups. Each patient in the four groups received 1 µg/kg i.v fentanyl. Patients in groups M, L and P are treated with 0.2 mg/kg i.v medazolam, 1.5mg/kg i.v lignocaine and 0.01mg/kg i.v propranolol respectively. Induction of anesthesia was then accomplished with 2mg/kg thiopental sodium followed by1.5mg/kg succinylcholine. Tracheal intubation was performed 2 minutes after induction of anesthesia. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product were measured before induction, after induction and at 2, 4, 6 and 8 minutes after intubation. The results indicated no significant variation in the hemodynamic pressor response in all four groups with tracheal intubation. In conclusion, a minimum effective dose of i.v pre-medications (fentanyl, medazolom, lignocaine and propranolol) were found to be individually successful in attenuating and providing a reliable control of all hemodynamic response changes accompanied the process of laryngoscopy and intubation. Therefore, all are proved effective premedication and no one being superior.

Key words: fentanyl, medazolom, lignocaine, propranolol, endotracheal intubation, hemodynamic response.

الخلاصة

يعتبر تنظير الحنجرة والقصبة الهوائية وكذلك التنبيت محفز غزوي أثناء التخدير , كلاهما يثير ردود أفعال القلب والأوعية الدموية التي تشمل ارتفاع ضغط الدم وعدم انتظام ضربات القلب وخلل النظم , وقد استخدمت أساليب مختلفة من شأنها أن تحد أو تخفف ردود الفعل من هذا القبيل . لقد تم تصميم هذه الدراسة لتقييم تأثير كل من الميدازولام , اليكنوكين والبروبرانولول باعتبارها مواد مساعدة ذات قيمة للفنتانيل في الدورة الدموية لتخفيف ردود الفعل غير المرغوب فيها خلال عملية التنبيت الرغامي للمرضى ذو الضغط الطبيعي . تم التوزيع العشوائي لاثنين وثلاثين حالة صنفت اعتماداً على نظم الجمعية الامريكية لأطباء التخدير , حال الأول أو الثاني من المرضى , من الذين تقرر إجراء عملية جراحية لهم تحت التخدير العام بالانتخاب القياسي . تم تقسيمهم إلى أربع مجاميع (8 مرضى في كل مجموعة) ، ورمز لهم بالأحرف فاء ، ميم ، لام وياء . تلقى كل مريض في الأربع مجموعات 1 ميكروغرام / كغم من الفنتانيل وريديا . وتعالج المرضى في مجموعات ميم ، لام ، ياء بمقدار 0.2 ملغم / كغم ميدازولام وريديا 1.5 ملغم /كغم لكنوكين وريديا 0.01 ملغم / كغم بروبرانولول وريديا على التوالي . تم بعدها استقراء التخدير مع 2 ملغم /كغم من الصوديوم ثايوبنتون يتبعه 1.5ملغم /كغم من السكسنيل كولين .نفذ التنبيت الرغامي بعد 2 دقيقة من تحريض التخدير ، وتم قياس معدل نبضات القلب وضغط الدم الانقباضي ، ضغط الدم الانبساطي ، الضغط الشرياني ومعدل ضغط المنتج قبل الاستقراء ، وذلك عند الحث ثم بعد 2 ، 8، 6، 4 دقائق بعد التنبيت ، أوضحت النتائج عدم وجود اختلاف كبير في استجابة إثارة ردود القلب أو الدورة الدموية في جميع الفئات الأربعة أثناء تنبيت القصبة الهوائية . في الختام تبين إن جرعة الحد الأدنى الفعالة من قبل الأدوية الأربعة (الفنتانيل ، الميدازولام ، الكنوكين والبروبرانولول) ناجحة في تخفيف حدة جميع التغيرات التي تصاحب عملية تنظير الحنجرة والتنبيت وتوفير مراقبة موثوق بها لذا فكل من هذه المواد المساعد تعتبر مفضلة وليس هنالك من هو أفضل من الآخر بينهما .

Introduction

Laryngoscopy and intubation are mandatory for most patients undergoing surgery under general anesthesia, often accompanied by a hemodynamic pressor response [1,2,3]. The rise in pulse rate and blood pressure is usually transient, variable and unpredictable; these changes are usually tolerated by healthy individuals, however, they may be deleterious in patients with hypertension, coronary artery diseases or intracranial hypertension, culminating perioperative myocardial ischemia, cardiac arrhythmias, acute heart failure and cerberovascular accident[4].

1Corresponding author E- mail : may_sabbagh @ yahoo.com
Received : 13/4/2010
Accepted : 8/6/2010

Various drugs including calcium channel blockers [5], vasodilators [6], β-adrenergic blockers [7,8], topical and intravenous lignocaine [9,10], opioids [11,12] and deep inhalational anesthesia [13,14] have been used in an attempt to attenuate or prevent pressor responses that accompanied endotracheal intubation, but non have been satisfactory. Fentanyl, a synthetic opioid, is one of the potent analgesics, when used before induction helps to attenuate hemodynamic response to intubation [1]. Medazolam, a short acting benzodiazepine, most commonly used for its anxiolytic, muscle relaxant and sedative properties [15,16], has slow onset of action with more gradual effects on circulation and greater degree of antegrade amnesia than thiopental; so it may offer an advantage in situation where hemodynamic stability is crucial [17,18]. Recent studies suggested that propranolol and osmolol can also provide consistent and reliable protection against the increase in both heart rate and systolic blood pressure that accompany intubation, and may reduce the risk of adverse cardiac events in patient undergoing major surgical operation [8,19]. Lignocaine hydrochloride, an amine ethylamide local anesthetic and class I B-antidysrrhythmic drug is also acceptable for attenuation of cardiovascular response to intubation, and can also diminish cough reflexes, dysrhythmias and increase in intracranial pressure [4]. The present study was designed to evaluate the effects of medazolam, lignocaine and propranolol, as adjuvants to fentanyl, on the hemodynamic pressor response during endotracheal intubation in normotensive patients.

Patients and Methods

The present study was conducted at the Neurosurgery Hospital in Baghdad in 2007 and involved thirty two ASA physical status I or II patients, with age range of 18-45 years, scheduled for elective surgery, requiring general anesthesia with endotracheal intubation. Patients with abnormal electrocardiogram, significant bronchospastic, neurologic or cardiovascular diseases, including those receiving medication known to affect blood pressure and heart rate were excluded. On arrival to the operating room, electrocardiograph monitoring, pulseoximetry and noninvasive arterial blood pressure monitoring were applied, and baseline values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and the rate pressure product (RPP) were obtained. Patients were randomly allocated into four groups (each include 8 patients) treated as follow: group F considered as control received only 1µg/kg i.v fentanyl, group M; patients in this group received 1µg/kg i.v fentanyl plus 0.2mg/kg i.v medazolam, group L; received both 1µg/kg i.v fentanyl and 1.5mg/kg i.v lignocaine, while group P received 1µg/kg i.v fentanyl together with 0.01mg/kg i.v propranolol. After 2 minutes of administrating pre-medications, induction of anesthesia was achieved with 2mg/kg thiopental and 1.5 mg/kg succinylcholin (all steps and doses were utilized according to the guidelines adopted in the neurosurgery hospital, Baghdad). After loss of eyelash reflex, the lungs were manually ventilated with oxygen. Direct laryngoscopy was performed at 2 minutes and trachea was intubated with proper sized disposable cuffed tube and fixed after confirmation of proper position. Following intubation, anesthesia was maintained with O_2, 1% halothane and pancuronium according to the requirements of surgery. The follow up of targeted parameters was started after administration of pre-anesthetic medications up to 8 minutes later on. HR, SBP, DBP and MAP were recorded before and after induction, then after intubation every 2 minutes for 8 minutes interval. The rate pressure product (RPP) was calculated by multiplying SBP by HR [20]. The data were statistically evaluated utilizing paired Student's ***t***-test to compare pre- and post-treatment values. Intergroup comparison was performed using unpaired ***t***-test and ANOVA. Results were considered significantly different at $P<0.05$.

Results

Demographic data of included patients are shown in table 1. No significant differences reported among groups with respect to sex, age, weight, hemoglobin (Hb), and hematocrit (HCT) values. The changes in hemodynamic variables from pre-induction (baseline values), at induction and after intubation in all groups (F, M, L and P) were shown in tables 2-6. After induction of anesthesia, SBP, DBP, MAP, HR and RPP showed less variation from the baseline values in the four groups. They slightly decreased, increased or remained unchanged, but no significant differences were reported. Tracheal intubation produces non-significant increase in SBP, DBP and MAP in all groups at 2 minutes after intubation. All parameters gradually, but non significantly, decreased with each 2 minutes increment until 8 minutes post intubation, with some exception like in L group, in which there was non significant increase in DBP and MAP at 6 minutes after intubation. Compared to base line values, both HR and RPP showed gradual but non significant increase at 2, 4, 6 and 8 minutes after intubation and reach optimal value at 6-8 minutes of intubation in all groups.

Table 1: Demographic data of patients included in the present study

Groups	Sex	Age (year)	Weight (kg)	Hb (%)	HCT (%)
Gr F (n=8)	6 M 2 F	25.8 ± 8.2 NS	64.0 ± 11.6 NS	13.0 ± 1.7 NS	41.1 ± 5.1 NS
Gr M (n=8)	5 M 3 F	25.6 ± 7.4 NS	64.6 ± 13.9 NS	12.1 ± 1.5 NS	37.0 ± 4.7 NS
Gr L (n=8)	6 M 2 F	27.6 ± 9.0 NS	64.1 ± 18.2 NS	13.1 ± 1.1 NS	38.0 ± 4.2 NS
Gr P (n=8)	6 M 2 F	28.0 ± 9.4 NS	61.9 ± 13.6 NS	13.1 ± 1.5 NS	39.4 ± 5.2 NS

F: Fentanyl group; M: Medazolam group; L: Lignocaine group; P: Propranolol group; Data are presented as mean ± SD; n=number of patients. NS: non significant

Table 2: Effects of Fentanyl or its combination with Medazolam, Lignocaine or Propranolol on systolic blood pressure during intubation in surgery

Stages		**Systolic Blood Pressure (mmHg)**			
		Groups			
		F	**M**	**L**	**P**
Pre-induction (base line)		129.8 ± 22.4[a]	135.5 ± 15.1[a,b]	125.5 ± 21.5[a]	137.4 ± 10.5[b]
Induction		121.3 ± 21.2[a,b]	129.6 ± 15.7[a,b]	126.3 ± 20.8[a]	134.6 ± 10.2[b]
Post-intubation	**2 min**	126.1 ± 20.7[a]	140.9 ± 20.1[a]	132.0 ± 20.0[a]	139.4 ± 10.7[a]
	4 min	117.3 ± 11.1[a]	127.8 ± 16.3[a,b]	127.5 ± 21.2[a,b]	134.3 ± 13.1[b]
	6 min	116.4 ± 8.4[a]	124.4 ± 23.1[a]	130.9 ± 26.0[a]	132.0 ± 33.8[a]
	8 min	110.8 ± 26.3[a]	113.8 ± 24.6[a]	117.9 ± 21.9[a]	128.6 ± 23.2[b]

Data are presented as mean ± SD; number of patients was 8 in each group; no significant difference existing with respect to induction value; non-identical superscripts (a,b) within the same time represent significant difference (P<0.05)

Table 3: Effects of Fentanyl or its combination with Medazolam, Lignocaine or Propranolol on diastolic blood pressure during intubation in surgery

Stages		**Diastolic Blood Pressure (mmHg)**			
		Groups			
		F	**M**	**L**	**P**
Pre-induction (base line)		72.4 ± 11.9[a]	75.4 ± 11.8[a,b]	74.4 ± 9.6[a]	78.6 ± 3.8[b]
Induction		69.6 ± 12.5[a]	72.4 ± 10.3[a]	75.1 ± 12.7[a]	76.6 ± 6.1[a]
Post-intubation	**2 min**	71.6 ± 13.0[a]	84.5 ± 14.6[a,b]	73.4 ± 10.1[a]	81.8 ± 8.5[b]
	4 min	70.8 ± 16.8[a,b]	78.3 ± 14.6[a,b]	67.3 ± 11.2*[a]	78.8 ± 6.0[b]
	6 min	70.6 ± 9.8[a]	74.4 ± 10.8[a]	87.3 ± 33.5[a]	75.1 ± 15.8[a]
	8 min	69.0 ± 9.9[a,b]	63.6 ± 14.1[a,b]	62.8 ± 17.0[b]	78.9 ± 16.9[a]

Data are presented as mean ± SD; number of patients was 8 in each group;
**P*<0.05 with respect to induction value; non-identical superscripts (a,b) within the same time represent significant difference (*P*<0.05)

Table 4: Effects of Fentanyl or its combination with Medazolam, Lignocaine or Propranolol on mean arterial pressure during intubation in surgery

Stages		Mean Arterial Pressure (mmHg)			
		Groups			
		F	M	L	P
Pre-induction (base line)		93.6 ± 12.7^{a}	97.9 ± 12.9^{a}	91.8 ± 12.2^{a}	98.5 ± 8.5^{b}
Induction		90.0 ± 13.3^{a}	96.0 ± 17.2^{a}	93.1 ± 12.9^{b}	96.4 ± 18.3^{c}
Post-intubation	2 min	94.5 ± 22.4^{a}	101.3 ± 30.3^{a}	95.4 ± 10.6^{b}	100.1 ± 8.6^{b}
	4 min	89.6 ± 15.7^{a}	96.6 ± 13.7^{a}	91.9 ± 13.4^{b}	98.3 ± 8.9^{b}
	6 min	88.9 ± 8.0^{a}	93.8 ± 14.2^{a}	99.4 ± 19.2^{a}	95.8 ± 21.9^{a}
	8 min	83.8 ± 13.9^{a}	82.5 ± 14.3*^{a}	82.6 ± 16.5^{a}	94.4 ± 25.4^{a}

Data are presented as mean ± SD; number of patients was 8 in each group; *$P<0.05$ with respect to induction value; non-identical superscripts (a,b,c) within the same time represent significant difference ($P<0.05$)

Table 5: Effects of Fentanyl or its combination with Medazolam, Lignocaine or Propranolol on heart rate during intubation in surgery

Stages		Heart Rate (Beat/min)			
		Groups			
		F	M	L	P
Pre-induction (base line)		92.0 ± 32.6^{a}	97.5 ± 23.1^{a}	93.4 ± 29.8^{a}	95.5 ± 95.9^{a}
Induction		98.9 ± 40.6^{a}	103.1 ± 30.8^{a}	98.3 ± 33.2^{a}	101.3 ± 22.4^{a}
Post-intubation	2 min	101.5 ± 33.1^{a}	107.8 ± 24.6^{a}	100.1 ± 33.8^{a}	108.3 ± 24.3^{a}
	4 min	122.0 ± 39.2*^{a}	118.0 ± 29.6^{a}	111.8 ± 25.2^{a}	109.3 ± 24.3*^{a}
	6 min	149.0 ± 36.4*^{a}	128.4 ± 29.9*^{a,b}	122.1 ± 35.0^{a,b}	117.1 ± 21.4*^{b}
	8 min	136.5 ± 36.8*^{a}	123.5 ± 30.1^{a}	134.5 ± 21.2*^{a}	124.6 ± 8.6*^{a}

Data are presented as mean ± SD; number of patients was 8 in each group; *$P<0.05$ with respect to induction value; non-identical superscripts (a,b) within the same time represent significant difference ($P<0.05$)

Table 6: Effects of Fentanyl or its combination with Medazolam, Lignocaine or Propranolol on rate pressure product during intubation in surgery

Stages		Rate Pressure Product			
		Groups			
		F	M	L	P
Pre-induction (base line)		11953 ± 4322^{a}	13224 ± 3441^{a}	11929 ± 5196^{a}	13232 ± 4772^{a}
Induction		11973 ± 4850^{a}	13450 ± 4448^{a}	12580 ± 5421^{a}	13673 ± 3558^{a}
Post-intubation	2 min	12814 ± 4557^{a}	15429 ± 5200^{a}	13362 ± 5801^{a}	15253 ± 4225^{a}
	4 min	14121 ± 4253^{a}	15269 ± 4901^{a}	14192 ± 3845^{a}	14772 ± 3866 *^{a}
	6 min	17360 ± 4501*^{a}	15946 ± 4440^{a}	16394 ± 6997^{a}	15549 ± 5354^{a}
	8 min	15452 ± 6082^{a}	14231 ± 4754^{a}	15806 ± 3779*^{a}	15957 ± 2646^{a}

Data are presented as mean ± SD; number of patients was 8 in each group; *$P<0.05$ with respect to induction value; non-identical superscripts (a,b) within the same time represent significant difference ($P<0.05$)

Discussion

Laryngoscopy and tracheal intubation produced stressful hemodynamic changes in the form of hypertension and tachycardia, attributed to increase in the circulating levels of catecholamines [21,22]. Control of such hemodynamic changes are very important to prevent detrimental effects, and the need for safe and effective therapeutic agents that may attenuate, blunt, suppress or abolish such changes became an important intervention during surgical procedures under general anesthesia. The results obtained from the present study revealed that all studied patients groups showed quantitatively and qualitatively similar hemodynamic pressor response at induction, intubation and post-intubation; the differences, if present, failed to reach statistically significant values. In the present study, failure to predict superiority for each pattern of drug intervention may be attributed to the limited number of patients in each group, and increase the number of patients may lead to more predictable values. However, pre-operative use of minimum effective doses of pre-anesthetic medications (1µg/kg fentanyl, 0.2mg/kg medazolam, 1.5mg/kg lignocaine and 0.01mg/kg propranolol) in the present study was found to be effective in restricting the non-significant increase in SBP, DBP and MAP values during short period of time (up to 2 minutes post-intubation), then each parameter start to decrease gradually (but non-significantly) until 8 minutes post- intubation; this means that all studied medications produce consistent and reliable protection against the abnormal increase in hemodynamic pressor response during laryngoscopy and intubation, similar to observations reported by other investigators [4,8,19,23]. Additionally in the present study, a non-significant increase in mean pulse rate and rate pressure product (good indicator for oxygen consumption) was reported in all groups of operated patients, starting from intubation and reach optimal values after 6-8 minutes post-intubation; this could be explained by the fact that surgical intervention usually starts after 6-8 minutes post-intubation, which is by itself a stressful procedure, predominantly suppresses the pressor response more effectively than tachycardia as a response [24]. Light anesthesia (fewer drugs by the intravenous route or via inhalational means) is claimed to be the major factor responsible for pre-operative awareness and hemodynamic instability [17]; to overcome this problem, fentanyl and/or medazolam are administered for the purpose of analgesia, sedation and anxiolysis [16]. Many evidence indicated that each of them, when used alone or in combination, enables reduction of the thiopental dose required to produce induction, and consequently limit potential side effects and help in attenuating the hemodynamic response to laryngoscopy and intubation [16,25,26]. Despite the potential advantages of the drug combination, reluctance to incorporate medazolam during light anesthesia persists due to concern regarding the potential for prolonged recovery [27,28]. However, a small pre-induction bolus dose of medazolam utilized in the present study did not prolong both recovery and discharge time from the day care unit following general anesthesia; this can be explained by the fact that the effects of medazolam on CNS is dose dependent [27]. In the present study, although fentanyl was administrated in relatively small doses, it produces sufficient analgesia for short surgical procedures, and no one of the operated patients experienced pain of relatively long duration or great severity. Although there is a possibility that administration of narcotic analgesic like fentanyl may affect pharmacokinetics of the anesthetic agents during induction, which is mostly due to changes in hemodynamic response [29,30,31], the patients in F and M groups showed non-significant increase in HR and RPP during laryngoscopy up to 6 minutes post-intubation; this increase seems to be suppressed in medazolam-treated group compared to fentanyl-treated group. This indicates that administration of medazolam before induction lead to hemodynamic stability most probably by mutual potentiation[32].Many studies have reviewed the effect of lignocaine to blunt the hemodynamic response after endotracheal intubation [4]. It has been reported that the strength and timing of lignocaine administration are equally important to prevent hemodynamic changes [33], however, irrespective of the dose and time of administration of lignocaine, there are still significant increase in hemodynamic parameters after intubation [34]. Kindler *et al* and Durrani *et al* reported that i.v. administration of 1.5mg/kg lignocaine did not prevent the increase in hemodynamic response associated with laryngoscopy and intubation [35,36]. Meanwhile, other investigators reported that 1.5mg/kg lignocaine effectively blocked the increase in SBP, DBP and HR after intubation [4,9]. In the present study, i.v administration of 1.5mg/kg lignocaine, 2 minutes before intubation provide reliable protection against the rise in hemodynamic response that associated with intubation process; this result was in accordance with many previously reported data, but not consistent with others [4,9]. Such effect may be attributed to rapid equilibration of lignocaine between blood and brain with production of sedative effect when administrated in appropriate dose [37]. Blocking and blunting adrenergic responses of tracheal intubation is the key pathophysiological step connecting β-blockers. Most of the studies concerned with evaluating the benefit of β-blockade on mortality and myocardial ischemia after tracheal intubation are based on using ultra-short acting selective β-blockers [38,39], while very limited reports were available about using propranolol in this respect [19]. In the present study, 0.01mg/kg i.v propranolol was used, and no significant differences were reported in HR and RPP between patients groups. Even a slight rise in HR and RPP that occurs at 6 minutes postintubation (a time of surgical intervention) was non significantly slowered in the β-blockade group in compare to other groups. These results are in accordance with those reported by Hussain *et al* and Yutaka *et al* [7,39]. The results of the present study shed a light on the possibility of using minimum doses of thiopental sodium for induction and maintenance of light anesthesia, for the aim of decreasing the time to discharge the patient from the recovery room and the day care unit; this situation seems to be compatible with the condition of shortage in medications required for anesthesia. In conclusion, minimum effective doses of pre-anesthetic medications (fentanyl, medazolam, lignocaine and propranolol) can maintain hemodynamic stability during laryngoscopy and intubation.

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