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Research Article

Attenuation of hemodynamic responses to endotracheal extubation: A prospective randomised controlled study between two different doses of Verapamil

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Abstract

Tracheal extubation causes significant hemodynamic stimulation resulting in transient increase in blood pressure and heart rate. This randomized, controlled, double blind study was conducted to compare the attenuation of hemodynamic responses to tracheal extubation in 150 patients of ASA I and II, undergoing elective surgery by using either verapamil 0.05 mg/kg or 0.1mg/kg with control group receiving saline. On completion of surgery, anaesthetic agents were discontinued, residual muscle relaxation reversed. The study drug was administered using double blind technique and patient extubated 2 minutes later. Changes in heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP) and rate pressure product (PR×SBP) were recorded during and after tracheal extubation. This study showed that both the doses of intravenous verapamil attenuated the increases in these variables. The inhibitory effect was greatest with verapamil 0.1 mg/ kg, while the alleviative effect of verapamil 0.05mg/ kg was inferior. These findings suggest that a bolus injection of verapamil 0.1 mg/kg given 2 min before tracheal extubation is a more effective prophylactic for attenuating the cardiovascular changes associated with extubation than 0.05mg/kg dose.

Keywords: Verapamil, Extubation, Hemodynamic response

1. Introduction

Problems associated with extubation, recovery and emergence are equally common as the problems at intubation; many aspects are controversial with no clear guidelines or protocols. Postoperative extubation of trachea is an important event in the course of general anaesthesia which causes a modest (10% to 30%) and transient (lasting approximately 5 to 15 minutes) increase in the HR and BP.[1-7] Normally these responses are transient in nature hence well tolerated by normo-tensive healthy subjects.

The exact mechanism responsible for these hemodynamic responses is unknown, it may be associated with release of catecholamine occurring during this stressful period.[7-10] Acute hemodynamic changes during extubation can lead to dangerous arrhythmias,[2-4] myocardial ischemia,[3-4,7,10-13] acute cardiac failure,[2,5,12] pulmonary edema[8] or cerebrovascular haemorrhage[14] in susceptible individuals. These responses can turn catastrophic in several situations like; ocular surgeries leading to dangerous increase in intraocular pressure;[15] patients with cardiac disease[3-4,10-12,16] or intracranial surgeries with raised intracranial pressure or for aneurysm surgeries[14] or with essential hypertension who show an exaggerated response to this stressful event.[13]

A number of attempts have been tried to attenuate these cardiovascular responses; such as extubation in deeper planes of anaesthesia,[17-18] avoiding or reducing duration of laryngoscopy before extubation[19], use of laryngeal mask airway instead of endotracheal tube,[20-22] topical airway anaesthesia with lignocaine,[23-26] intra-cuff or intravenous lignocaine[27-28]. Pre-treatment with intravenous beta blockers[29-33], small doses of intravenous narcotics like fentanyl or remifentanil prior to extubation[34-36] intravenous calcium channel blockers[37-41], use of vasodilators like nitrates, prostaglandins and magnesium sulphate[42-44] have been tried to overcome these issue. But only a handful of them have been proved beneficial in preventing the response. This is because, this response is multifactorial including pain of the wound, emergence from anesthesia, changes in body temperature, use of drugs to antagonize the neuromuscular block, shift from controlled ventilation to spontaneous ventilation and irritation caused by an endotracheal tube to the laryngotracheal mucosa.[40]

In the present study, we have attempted to evaluate and compare the ability of intravenous Verapamil (phenylalkylamine group of calcium channel blocker) in two different doses of 0.05 mg/kg and 0.1 mg/kg, 2 minutes prior to extubation in attenuating cardiovascular response to postoperative tracheal extubation with the placebo groupundergoing elective non-cardiac surgery under general anaesthesia.

2. Material and Methods

The present prospective randomised controlled double blind comparative study conducted between October 2011 to January 2013at Department of Anaesthesia, Jawaharlal Nehru Medical College, Wardha; comprising 150 patients of ASA status I and II in the age range of 20 to 60 years weighing 40 to 80 kg, scheduled for elective non-cardiac surgery and requiring general anaesthesia with endotracheal intubation for more than 1 hour. Approval from institutional ethical committee was taken and the study was commenced. A pre-procedural systemic clinical examination was done and written informed valid consent was obtained from all the patients enrolled for the study. All patients with refusal for enrolment, allergic to the study drug, laparoscopic surgery, difficult airways, history of hypertension, bronchospasm, cardiac arrhythmias, any cardiac disorder, or diabetes mellitus were excluded.

All the enrolled patients were randomly divided into three groups as control group (saline), group-I (IV verapamil 0.05 mg/kg) and group-II (IV verapamil 0.1 mg/kg) of 50 each. Preoperative and perioperative parameters like heart rate (HR), Systolic Blood Pressure (SBP), mean arterial pressure (MAP) were recorded and rate pressure product (PRXSBP = RPP) was calculated. After achieving intravenous access patient was pre-medicated followed by induction of anaesthesia, laryngoscopy and intubation.Those patients who required multiple attempts for intubation and duration of laryngoscopy more than 15 seconds were excluded from study. Patients were ventilated using a 40: 60 mixture of oxygen and nitrous oxide using Bain's circuit and controlled ventilation at flow rates of 100 ml/kg/min. Muscle relaxation was provided using IV Vecuronium in loading dose of 0.1 mg/kg followed by increments of 0.02 mg/kg and Sevoflurane was used as an inhalation agent for maintenance (between 1 to 2% dial setting) to maintain a target HR and SBP of ± 20% from base line.

The study drug was injected 2 minutes prior to the extubation i.e. either Verapamil (0.05 mg/kg or 0.1 mg/kg made to volume of 5 ml with normal saline) or normal saline 5 ml was injected over 30 seconds. The patients were divided randomly in 3 groups each consisting of 50 patients.Patients were given 100% oxygen between injection of drug and tracheal extubation. After oropharyngeal suction the tracheal tube was gently withdrawn. Quality of extubation was rated as 1: no cough or strain, 2: minimal coughing, 3: moderate coughing, 4: marked coughing or straining and 5: poor extubation with laryngospasm. The hemodynamic parameters were recorded at the time of extubation (T-0), one (T-1), three (T-3), five (T-5) and ten (T-10) minutes post extubation. The data was recorded and analysed with SPSS 18.0 and statistical analysis was done by one way analysis of variance (ANOVA), followed by Tukey's Multiple Comparison Test for parametric and nonparametric data; p-value of < 0.05 was considered as statistically significant.

3. Results

Majority of patients 78%, 70% and 86% of patients in control, group-I and group-II respectively, belonged to age group 21-50 years. The male: female sex ratio for control group 1:0.61, group-I 1:1.27 and group-II 1:1.38. Mean weight of the patient were comparable for all three groups, majority were in 41-60 kg range. (Table 1)

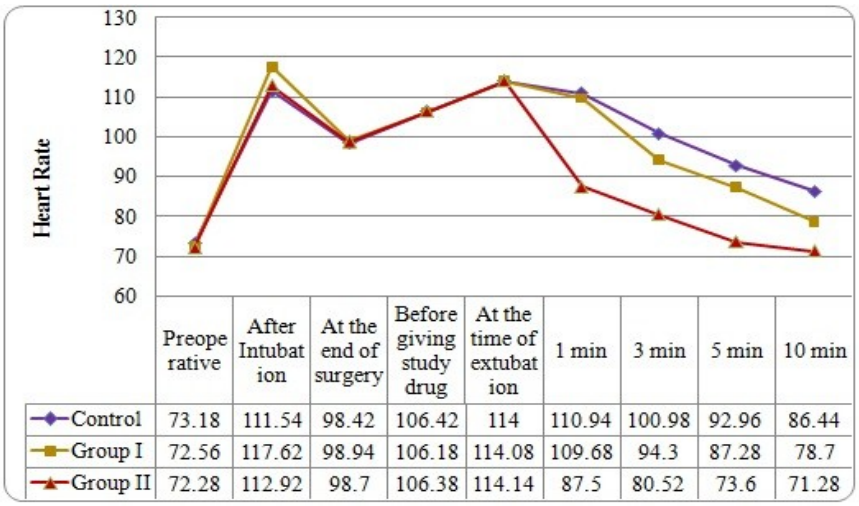
Table 1: Epidemiological details of patients

	Control	Group-I	Group-II
Age (Mean/ SD)	36.88 ±12.54	39.94±12.20	35.24±9.99
Gender			
Male	31(62%)	22(44%)	21(42%)
Female	19(38%)	28(56%)	29(58%)
Weight (Mean/ SD)	49.78±7.35	52.04±5.83	50.90±5.54

Prepoperative mean HR, SBP, MAP and RPP were comparable pre-operatively. Similarly no statistically significant difference was observed in any of these parameters till the time of extubation; however statistically significant decrease was observed at 1 minute post extubation in group-II when compared to control and group-I ($p<0.05$).At 3, 5 and 10 minutes after extubation both group-I and group-II showed statistically significant decrease in mean HR as compared to control group ($p<0.05$); however the fall was more in group-II as compared to group-I ($p<0.05$)(Figure 1& 2).

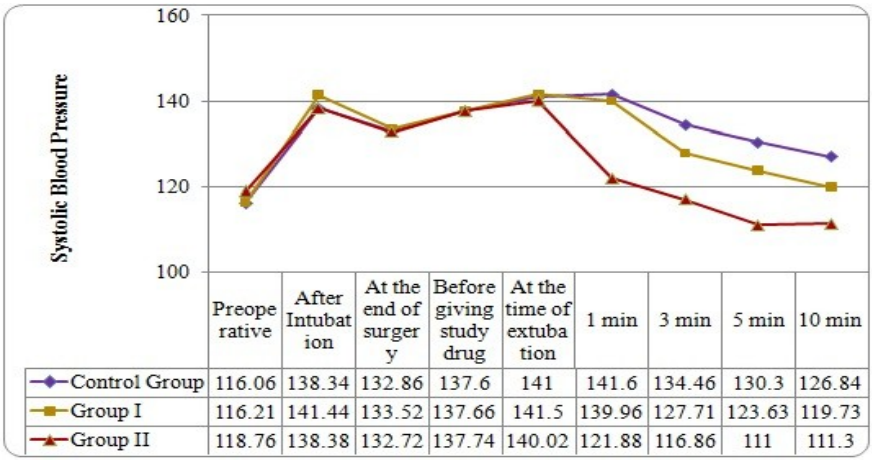
During the course of the study none of the patients in the study groups receiving verapamil developed profound hypotension [SBP <80 mmHg], bradycardia [HR < 50 beats/min], sinoatrial or atrioventricular block requiring sympathomimetic drugs during tracheal extubation or prolongation of time for extubation or recovery.

Figure 1: Comparison of changes in mean Heart Rate of the patients in three groups at various time intervals



	Preoperative	After Intubation	At the end of surgery	Before giving study drug	At the time of extubation	1 min	3 min	5 min	10 min
Control	73.18	111.54	98.42	106.42	114	110.94	100.98	92.96	86.44
Group I	72.56	117.62	98.94	106.18	114.08	109.68	94.3	87.28	78.7
Group II	72.28	112.92	98.7	106.38	114.14	87.5	80.52	73.6	71.28

Figure 2: Comparison of changes in mean SBP of the patients in three groups at various time intervals



	Preoperative	After Intubation	At the end of surgery	Before giving study drug	At the time of extubation	1 min	3 min	5 min	10 min
Control Group	116.06	138.34	132.86	137.6	141	141.6	134.46	130.3	126.84
Group I	116.21	141.44	133.52	137.66	141.5	139.96	127.71	123.63	119.73
Group II	118.76	138.38	132.72	137.74	140.02	121.88	116.86	111	111.3

3. Discussion

An anaesthesiologist quite frequently experience problems after tracheal extubation; tracheal intubation and its problems have received much attention as compared to tracheal extubation which has relatively been less emphasized. Though tracheal extubation seems to be a benign procedure, multiple studies have shown that it can cause significant increase in BP and HR which may persist till the recovery period.[1-6]

High degree of sympathetic stimulation, as evidenced by tachycardia, hypertension and increased levels of circulating catecholamines during extubation may prove to be detrimental to their health or to the successful outcome of surgery.Hypertensive subjects exhibit an exaggerated response to laryngoscopy and intubation as well as to awakening and extubation compared to normotensive patients.[7,13,45]Increase in BP, HR and RPP which is a multiple of SBP and HR increases the cardiac workload and the oxygen demand of the myocardium; increasing the risk of developing a fresh episode of myocardial ischemia and infarction in known patients of ischemic heart disease due to a fixed coronary blood flow, along with fall in cardiac index and ejection fraction.[3-4,10-12,16]Therefore, perioperative measurement of RPP is of vital importance.

Several researches have advocated the use of calcium channel blockers to control tachycardia and hypertension occurring during extubation.[37-41] However, IV verapamil has short onset of action of about 30 seconds, peak action in 2-3 minutes, brief duration of action due to rapid redistribution i.e. up to 15 minutes, excellent negative chronotropic and negative ionotropic effect, single bolus dose, selectivity towards cardiovascular system, easily stored and cost effective.[46-48]

Intravenous Verapamil is known to cause synergistic bradycardia and hypotension,[46-49]thismay however be a disadvantage in patients in whom cardiac depression is undesirable (e.g. those with congestive cardiac failure). However the study was conducted in ASA class I and II patients who are less likely to develop cardiac depression with the use of IV verapamil.Similarly, study was conducted till 10 minutes post-extubation period because of the fact that IV verapamil has rapid early redistribution in 4-5 minutes suggesting that adverse effects like hypotension and bradycardia are less likely to occur beyond the study period.[47-48]

After intubation significant rise in mean HR, SBP, MAP and RPP in all three groups were comparable to preoperative values; this response was expected as no prophylactic measure was taken to attenuate the tachycardia due to laryngoscopy and intubation[50] and at the end of the surgery and at the time of extubation also there was rise in all the parameters which were comparable in three groups.A single dose of 0.05 mg/kg or 0.1 mg/kg of verapamil given 2 minutes prior to extubation was able to attenuate this rise in HR, SBP , MAP and RPP as compared to control group; however 0.1mg/kg dose showed more significant attenuation. HR, SBP , MAP and RPP at extubation was reduced at 1 minute with 0.1mg/kg dose and at 3 minutes with 0.05mg/kg dose after extubation, similarly seen in study by Mikawa et al[38] which showed that alleviation of pressor response was greater with verapamil 0.1 mg/kg, while the effect of verapamil 0.05 mg/kg dose was inferior. These observations were also found in other studies supporting 0.1mg/kg dose of IV verapamil as safe and effective for reducing pressure response to extubation with no incidence of bradycardia or hypotension.[39,51-53]

Verapamil has negative dromotropic and ionotropic effects, vasodilating properties, ability to increase the P-R interval and produce AV block. In fact reflex activation of the sympathetic nervous system may be necessary during verapamil therapy to maintain normal conduction.[54] However, in our study, none of the patients receiving verapamil developed profound hypotension [SBP <80 mmHg], bradycardia [HR < 50 beats/min], sinoatrial or atrioventricular block requiring sympathomimetic drugs during tracheal extubation which is supported by various other studies.[39,55] Calcium channel blockers may, under certain circumstances, potentiate hemodynamic and MAC depressive effects of inhalation agents and the effects of neuromuscular blocking agents.[50] However in our study none of the patients showed delayed recovery from anesthesia which is supported by a study conducted by Kanayaet al.[56]This study showed that a therapeutic dose of nicardipine or verapamil could safely be given intravenously to the patients under vecuronium-induced neuromuscular blockade.

5. Conclusion

Thus, from our study we conclude that in patients with ASA physical status I and II intravenous bolus doses of verapamil 0.1 mg/kg and 0.05mg/kg given 2 minutes prior to extubation is a simple, safe, cheap and effective prophylactic

method for attenuating the hemodynamic responses to extubation with no noticeable adverse effects. However, the alleviation is greater with 0.1 mg/kg of IV verapamil than with 0.05mg/kg dose. Hence this drug is a useful adjunct to our therapeutic armamentarium.

References

1. Brock-Utne JG, Jaffe RA, Robins B, Ratner E. Difficulty in extubation. A cause for concern. *Anaesthesia.* Mar 1992;47(3):229-230.
2. Coriat P, Mundler O, Bousseau D, et al. Response of left ventricular ejection fraction to recovery from general anesthesia: measurement by gated radionuclide angiography. *Anesthesia and analgesia.* Jun 1986;65(6):593-600.
3. Hartley M, Vaughan RS. Problems associated with tracheal extubation. *British journal of anaesthesia.* Oct 1993;71(4):561-568.
4. Miller KA, Harkin CP, Bailey PL. Postoperative tracheal extubation. *Anesthesia and analgesia.* Jan 1995;80(1):149-172.
5. Paulissian R, Salem MR, Joseph NJ, et al. Hemodynamic responses to endotracheal extubation after coronary artery bypass grafting. *Anesthesia and analgesia.* Jul 1991;73(1):10-15.
6. Tomori Z, Widdicombe JG. Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. *The Journal of physiology.* Jan 1969;200(1):25-49.
7. Lowrie A, Johnston PL, Fell D, Robinson SL. Cardiovascular and plasma catecholamine responses at tracheal extubation. *British journal of anaesthesia.* Mar 1992;68(3):261-263.
8. Asai T, Koga K, Vaughan RS. Respiratory complications associated with tracheal intubation and extubation. *British journal of anaesthesia.* Jun 1998;80(6):767-775.
9. Kim JD, Kim KH. Survey of Postoperative Endotracheal Tube Extubation Practice.*Korean journal of anaesthesia.* Oct. 2007;53(4):477-485.
10. Elia S, Liu P, Chrusciel C, Hilgenberg A, Skourtis C, Lappas D. Effects of tracheal extubation on coronary blood flow, myocardial metabolism and systemic haemodynamic responses. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* Jan 1989;36(1):2-8.
11. Edwards ND, Alford AM, Dobson PM, Peacock JE, Reilly CS. Myocardial ischaemia during tracheal intubation and extubation. *British journal of anaesthesia.* Oct 1994;73(4):537-539.
12. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? *Anesthesiology.* Feb 1985;62(2):107-114.
13. Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. *British journal of anaesthesia.* Dec 1988;61(6):675-679.
14. Ogasawara K, Noda A, Yasuda S, Kobayashi M, Yukawa H, Ogawa A. Effect of calcium antagonist on cerebral blood flow and oxygen metabolism in patients with hypertension and chronic major cerebral artery occlusion: a positron emission tomography study. *Nuclear medicine communications.* Jan 2003;24(1):71-76.
15. Van Den Berg AA, Savva D, Honjol NM. Attenuation of the haemodynamic responses to noxious stimuli in patients undergoing cataract surgery. A comparison of magnesium sulphate, esmolol, lignocaine, nitroglycerine and placebo given i.v. with induction of anaesthesia. *European journal of anaesthesiology.* Mar 1997;14(2):134-147.
16. Wellwood M, Aylmer A, Teasdale S, et al. Extubation and Myocardial Ischemia. *Anesthesiology.* 1984;61(3):A132.
17. Conti J, Smith D. Haemodynamic responses to extubation after cardiac surgery with and without continued sedation. *British journal of anaesthesia.* Jun 1998;80(6):834-836.
18. Smith I, Taylor E, White PF. Comparison of tracheal extubation in patients deeply anesthetized with desflurane or isoflurane. *Anesthesia and analgesia.* Oct 1994;79(4):642-645.
19. Xue FS, Wang Q, Liao X, Yuan YJ. Cardiovascular intubation responses with Airway Scope and Macintosh laryngoscope. *Anaesthesia.* Apr 2012;67(4):434-435; author reply 435-436.
20. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Cardiovascular responses to tracheal extubation or LMA removal in children.

Canadian journal of anaesthesia = Journal canadien d'anesthesie. Feb 1998;45(2):178-181.

21. Fujii Y, Toyooka H, Tanaka H. Cardiovascular responses to tracheal extubation or LMA removal in normotensive and hypertensive patients. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* Oct 1997;44(10):1082-1086.
22. Idrees A, Khan FA. A comparative study of positive pressure ventilation via laryngeal mask airway and endotracheal tube. *JPMA. The Journal of the Pakistan Medical Association.* Oct 2000;50(10):333-338.
23. Jee D, Park SY. Lidocaine sprayed down the endotracheal tube attenuates the airway-circulatory reflexes by local anesthesia during emergence and extubation. *Anesthesia and analgesia.* Jan 2003;96(1):293-297.
24. Lee DH, Park SJ. Effects of 10% lidocaine spray on arterial pressure increase due to suspension laryngoscopy and cough during extubation. *Korean journal of anesthesiology.* Jun 2011;60(6):422-427.
25. Watkins J, Lee D, White WA, Jr., Mundy S. Effects of topical lidocaine on successful extubation time among patients undergoing elective carotid endarterectomies. *AANA journal.* Apr 2012;80(2):99-104.
26. Yamasaki H, Takahashi K, Yamamoto S, Yamamoto Y, Miyata Y, Terai T. Efficacy of endotracheal lidocaine administration with continuous infusion of remifentanil for attenuating tube-induced coughing during emergence from total intravenous anesthesia. *Journal of anesthesia.* May 7 2013.
27. Huang CJ, Hsu YW, Chen CC, et al. Prevention of coughing induced by endotracheal tube during emergence from general anesthesia--a comparison between three different regimens of lidocaine filled in the endotracheal tube cuff. *Acta anaesthesiologica Sinica.* Jun 1998;36(2):81-86.
28. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH. Blood-pressure and pulse-rate responses to endotracheal extubation with and without prior injection of lidocaine. *Anesthesiology.* Aug 1979;51(2):171-173.
29. Dyson A, Isaac PA, Pennant JH, Giesecke AH, Lipton JM. Esmolol attenuates cardiovascular responses to extubation. *Anesthesia and analgesia.* Dec 1990;71(6):675-678.
30. Kovac AL, Masiongale A. Comparison of nicardipine versus esmolol in attenuating the hemodynamic responses to anesthesia emergence and extubation. *Journal of cardiothoracic and vascular anesthesia.* Feb 2007;21(1):45-50.
31. Kross RA, Ferri E, Leung D, et al. A comparative study between a calcium channel blocker (Nicardipine) and a combined alpha-beta-blocker (Labetalol) for the control of emergence hypertension during craniotomy for tumor surgery. *Anesthesia and analgesia.* Oct 2000;91(4):904-909.
32. Shirasaka T, Iwasaki T, Hosokawa N, Komatsu M, Kasaba T, Takasaki M. Effects of landiolol on the cardiovascular response during tracheal extubation. *Journal of anesthesia.* 2008;22(3):322-325.
33. Wang YQ, Guo QL, Xie D. [Effects of different doses of esmolol on cardiovascular responses to tracheal extubation]. *Hunan yi ke da xue xue bao = Hunan yike daxue xuebao = Bulletin of Hunan Medical University.* Jun 2003;28(3):259-262.
34. Aouad MT, Al-Alami AA, Nasr VG, Souki FG, Zbeidy RA, Siddik-Sayyid SM. The effect of low-dose remifentanil on responses to the endotracheal tube during emergence from general anesthesia. *Anesthesia and analgesia.* Apr 2009;108(4):1157-1160.
35. Nishina K, Mikawa K, Maekawa N, Obara H. Fentanyl attenuates cardiovascular responses to tracheal extubation. *Acta anaesthesiologica Scandinavica.* Jan 1995;39(1):85-89.
36. Yoo YC, Na S, Jeong JJ, Choi EM, Moon BE, Lee JR. Dose-dependent attenuation by fentanyl on cough during emergence from general anesthesia. *Acta anaesthesiologica Scandinavica.* Nov 2011;55(10):1215-1220.
37. Kovac AL, McKinley C, Tebbe CJ, Williams C. Comparison of nicardipine versus placebo to control hemodynamic responses during emergence and extubation. *Journal of cardiothoracic and vascular anesthesia.* Dec 2001;15(6):704-709.
38. Mikawa K, Nishina K, Maekawa N, Obara H. Attenuation of cardiovascular responses to tracheal extubation: verapamil versus diltiazem. *Anesthesia and analgesia.* Jun 1996;82(6):1205-1210.
39. Mikawa K, Nishina K, Takao Y, Shiga M, Maekawa N, Obara H. Attenuation of cardiovascular responses to tracheal extubation: comparison of verapamil, lidocaine, and verapamil-lidocaine combination. *Anesthesia and analgesia.* Nov 1997;85(5):1005-1010.

40. Nishina K, Mikawa K, Maekawa N, Obara H. Attenuation of cardiovascular responses to tracheal extubation with diltiazem. *Anesthesia and analgesia.* Jun 1995;80(6):1217-1222.
41. Tsutsui T. Combined administration of diltiazem and nicardipine attenuates hypertensive responses to emergence and extubation. *Journal of neurosurgical anesthesiology.* Apr 2002;14(2):89-95.
42. Ferasatkish R, Dabbagh A, Alavi M, et al. Effect of magnesium sulfate on extubation time and acute pain in coronary artery bypass surgery. *Acta anaesthesiologica Scandinavica.* Nov 2008;52(10):1348-1352.
43. Nagatani A, Shibata O, Haseba S, et al. [The effect of nitroglycerin ointment on cardiovascular functions in hypertensive patients during emergence from anesthesia]. *Masui. The Japanese journal of anesthesiology.* Oct 1989;38(10):1312-1316.
44. Nishina K, Mikawa K, Shiga M, Maekawa N, Obara H. Prostaglandin E1 attenuates the hypertensive response to tracheal extubation. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* Jul 1996;43(7):678-683.
45. Fujii Y, Kihara S, Takahashi S, Tanaka H, Toyooka H. Calcium channel blockers attenuate cardiovascular responses to tracheal extubation in hypertensive patients. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* Jul 1998;45(7):655-659.
46. Durand PG, Lehot JJ, Foex P. Calcium-channel blockers and anaesthesia. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* Jan 1991;38(1):75-89.
47. McTavish D, Sorkin EM. Verapamil. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. *Drugs.* Jul 1989;38(1):19-76.
48. McAllister RG, Jr. Clinical pharmacology of slow channel blocking agents. *Progress in cardiovascular diseases.* Sep-Oct 1982;25(2):83-102.
49. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. *The American journal of cardiology.* Dec 1 1980;46(6):1047-1058.
50. Kim JH, Lee YS, Kim WY, et al. Effect of nicardipine on haemodynamic and bispectral index changes following endotracheal intubation. *The Journal of international medical research.* Jan-Feb 2007;35(1):52-58.
51. Nishina K, Mikawa K, Takao Y, Shiga M, Maekawa N, Obara H. Prostaglandin E1, lidocaine, and prostaglandin E1-lidocaine combination for attenuating cardiovascular responses to extubation. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* Nov 1997;44(11):1211-1214.
52. Ryu JH, Apfel CC, Whelan R, et al. Comparative prophylactic and therapeutic effects of intravenous labetalol 0.4 mg/kg and nicardipine 20 mug/kg on hypertensive responses to endotracheal intubation in patients undergoing elective surgeries with general anesthesia: a prospective, randomized, double-blind study. *Clinical therapeutics.* Mar 2012;34(3):593-604.
53. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon heart. *Surg Gynaec Obst* 1940 ; 70:157-62.
54. Chen CC, Tsai PS, Yang LC, Jawan B, Lee JH. The comparative potency of intravenous nicardipine and verapamil on the cardiovascular response to tracheal intubation. *Acta anaesthesiologica Sinica.* Dec 1996;34(4):197-202.
55. Morimoto Y, Kemmotsu O, Gando S, Shibano T, Shikama H. The effect of calcium channel blockers on cerebral oxygenation during tracheal extubation. *Anesthesia and analgesia.* Aug 2000;91(2):347-352.
56. Jenkins LC, Scoates PJ. Anaesthetic implications of calcium channel blockers. *Canadian Anaesthetists' Society journal.* Jul 1985;32(4):436-447.
57. Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? *Anesthesiology.* May 1988;68(5):676-680.