Prostaglandin E_1, lidocaine, and prostaglandin E_1-lidocaine combination for attenuating cardiovascular responses to extubation

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Purpose: Tracheal extubation produces haemodynamic changes that may cause myocardial ischaemia in patients with coronary arterial disease. Intravenous infusion of prostaglandin E1 (PGE_1) attenuated the hypertensive response to tracheal extubation but failed to blunt the tachycardia, which was attenuated by intravenous lidocaine. Thus, we investigated whether a combination of PGE_1 and lidocaine can overcome the drawbacks of treatment with PGE_1 alone.

Methods: One hundred adult patients (ASA I) undergoing elective minor surgery were randomly assigned to receive one of four treatments: saline (as a control), 1 $mg \cdot kg^{-1}$ lidocaine, infusion of 0.1 $\mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$ PGE_1, or infusion of 0.1 $\mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$ PGE_1 plus injection of 1 $mg^{-1} \cdot kg^{-1}$ lidocaine. Lidocaine was injected two minutes before tracheal extubation. The PGE_1 was infused from completion of surgery until five minutes after tracheal extubation. Anaesthesia was maintained with sevoflurane 1.0%–2.5% and nitrous oxide 60%. Heart rate (HR) and blood pressure (BP) were measured before and after tracheal extubation.

Results: Lidocaine alone and PGE_1-lidocaine combination attenuated the increases in BP and HR observed in the control group: PGE_1 alone was effective in attenuating hypertensive response but ineffective for tachycardia. The suppressive effect of the PGE_1-lidocaine combination on BP increase was superior to that of each drug alone, and the combined effect on HR increase was similar to that of lidocaine alone.

Conclusion: The combination of PGE_1 infusion and lidocaine is a more effective method of attenuating hypertension and tachycardia associated with tracheal extubation than either drug alone.

Objectif : Les changements hémodynamiques provoqués par l'extubation de la trachée peuvent induire de l'ichémie myocardique chez les insuffisants coronariens. On a montré que la perfusion intraveineuse de prostaglandine E_1 (PGE_1) atténuait la réaction hypertensive à l'extubation sans dimunier la tachycardie qui répond à la lidocaïne intraveineuse. Nous avons recherché si l'association PGE_1-lidocaïne pouvait surmonter les inconvénients de la PGE_1 seule.

Méthodes : Cent adultes (ASA I) opérés pour une chirurgie mineure non urgente ont été répartis aléatoirement pour recevoir un des quatre traitements suivants : sol.phys. (contrôle), lidocaïne 1 $mg \cdot kg^{-1}$, PGE_1 0,1 $mg \cdot kg^{-1} \cdot min^{-1}$ en perfusion, ou PGE_1 0,1 $mg \cdot kg^{-1} \cdot min^{-1}$ en perfusion avec une injection de lidocaïne 1 $mg \cdot kg^{-1}$ deux minutes avant l'extubation. La perfusion de PGE_1 débutait à la fin de la chirurgie et finissait après l'extubation. L'anesthésie était entretenue avec du sévoflurane 1,0%–2,5% et du protoxyde d'azote 60%. On mesurait la fréquence cardiaque (FC) et la tension artérielle (TA) avant et après l'extubation.

Résultats : La lidocaïne seule et l'association PGE_1-lidocaïne atténuaient l'augmentation de la TA et de la FC observée dans le groupe contrôle ; la PGE_1 seule atténuait efficacement la réaction hypertensive mais non la tachycardie. L'association PGE_1-lidocaïne contrôlait mieux l'élévation de la TA que l'un ou l'autre des deux produit administrés seuls, et avait un effet identique à la lidocaïne seule sur l'augmentation de la FC.

Conclusion : Une perfusion de PGE_1 associée à de la lidocaïne atténue plus efficacement l'hypertension et la tachycardie provoquées par l'extubation de la trachée que l'un ou l'autre des produits administré seul.

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TRACHEAL intubation often provokes hypertension and tachycardia,[1] which may cause dangerous increases in myocardial oxygen demand in patients with coronary arterial disease (CAD).[1] Many drugs have been recommended to control these haemodynamic events, including lidocaine, fentanyl, diltiazem, and verapamil.[2-5] Infusion of prostaglandin E_1 (PGE_1) attenuated the hypertension during tracheal extubation more effectively than did lidocaine.[6] However, PGE_1 failed to blunt tachycardia in this setting. In contrast, lidocaine successfully attenuated tachycardic responses.[6] Many types of noxious stimuli during this period are likely to be involved in these complications including emergence from anaesthesia and laryngeal irritation. Since pharmacological mechanisms for the control of the haemodynamic changes during tracheal extubation are thought to be different with PGE_1 and lidocaine, a combination of these drugs may elicit additive prophylactic effects for this purpose; in particular, the failure of PGE_1 to suppress tachycardia may be surmounted by the concomitant use of lidocaine. To test this hypothesis, we compared the effect of the combination of PGE_1 infusion and lidocaine injection with that of each drug alone. We used ASA I patients to avoid the potential risk of sequelae due to excessive hypotension caused by the combination of PGE_1 and lidocaine.

Methods

After institutional approval and written informed consent, we studied 100 adult patients (ASA I) undergoing elective surgery. They were excluded if they suffered from co-existing systemic illness, untreated hypertension, or allergies to the study medications, and were taking cardiovascular or antihypertensive medications. The patients were randomly assigned to receive one of four treatments: Group S=saline (control), Group L=1 $mg \cdot kg^{-1}$ lidocaine, Group PG=0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 (Prostandin®, Ono, Japan), and Group PG-L=0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 plus 1 $mg \cdot kg^{-1}$ lidocaine. Saline (Groups S and L) or PGE_1 (Groups PG and PG-L) *iv* infusion was started from the end of surgery and continued until five minutes after tracheal extubation using an infusion pump (Terufusion STC-523, Terumo, Japan). Saline (Groups S and PG) or lidocaine (Groups L and PG-L) *iv* was given (over five seconds) two minutes before tracheal extubation. These medications were provided in coded, labeled syringes.

Premedication consisted of 4–6 mg diazepam *po* and 0.5 mg atropine *im*. An epidural catheter was placed preoperatively, but no drugs were administered via this route until final haemodynamic data were obtained. Anaesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopentone and 2 $\mu g \cdot kg^{-1}$ fentanyl and tracheal intubation was facilitated with 0.2 $mg \cdot kg^{-1}$ vecuronium. Anaesthesia was maintained with sevoflurane 1.0%–2.5% and nitrous oxide (N_2O) 60% in oxygen. The concentration of end-tidal sevoflurane and N_2O were monitored throughout anaesthesia (Capnomac Ultima®, Datex, Finland). Blood pressure (BP) was recorded every three minutes during surgery using an automated noninvasive BP monitor with printer (Pulsemate BX-5®, Nippon Colin, Tokyo, Japan). Heart rate (HR) was monitored by ECG with an automatic arrhythmia detector. Muscle relaxation was maintained by intermittent injections of 0.02 $mg \cdot kg^{-1}$ vecuronium. At the end of surgery, sevoflurane and N_2O were discontinued, and residual muscle relaxation was reversed with 0.05 $mg \cdot kg^{-1}$ neostigmine and 0.02 $mg \cdot kg^{-1}$ atropine. Recovery from muscle relaxation was assessed by hand grip. The trachea was extubated three minutes after the completion of surgery. Immediately before tracheal extubation, we confirmed that the concentration of end-tidal sevoflurane had decreased to $\geq 0.1\%$ and the patients could breathe spontaneously and open their eyes on command. Oropharyngeal secretions were aspirated prior to extubation. After tracheal extubation, oxygen 100% was given *via* a face mask for five minutes.

Systolic BP (SBP), diastolic BP (DBP), and HR were measured every minute after surgery. Haemodynamic data obtained from the end of surgery (i.e., baseline) until 10 min after extubation were analyzed for cardiovascular changes associated with tracheal extubation: points for analysis included at the end of surgery, two minutes and one minute before tracheal extubation, at tracheal extubation, and at one, five and ten minutes after tracheal extubation. Peak SBP, DBP, and HR values during this period were also recorded. The haemodynamic data were compared among the four groups and with baseline values within individual study groups. The quality of tracheal extubation was evaluated using a five point rating scale.[3]

Statistical analysis was performed using two-way analysis of variance followed by Bonferroni modification of t test for parametric data, and Kruskal-Wallis test and chi-squared test for nonparametric data. $P < 0.05$ was deemed significant.

Results

Of 131 patients enrolled in the study, 31 were excluded from analysis due to nonfulfilment of the study protocol; failure of tracheal extubation two minutes after lidocaine or saline injection (7, 12, 7 and 5 patients in Groups S, L, PG, and PG-L, respectively). No differences were observed among the four groups with respect to patient or surgical data (Table I). The SBP, DBP, and HR in

TABLE I Data on patients and surgery (mean ± SEM).

	Group S	*Group L*	*Group PG*	*Group PG-L*
n	25	25	25	25
Male/Female	4/21	7/18	6/19	7/18
Age (yr)	38 ± 1.4	41 ± 1.8	40 ± 1.5	37 ± 1.6
Weight (kg)	57 ± 1.9	59 ± 2.0	59 ± 1.8	61 ± 2.1
Height (cm)	162 ± 1.6	165 ± 2.2	164 ± 1.8	165 ± 2.3
Preoperative Haemodynamics				
– SBP (mmHg)	129 ± 2.8	123 ± 2.7	125 ± 2.6	128 ± 2.5
– DBP (mmHg)	80 ± 1.9	76 ± 1.7	76 ± 1.8	77 ± 1.8
– HR (beats/min)	76 ± 1.7	73 ± 1.7	75 ± 1.6	77 ± 1.7
Duration of anaesthesia (min)	177 ± 6.5	184 ± 7.1	170 ± 6.1	181 ± 6.5
Duration of surgery (min)	138 ± 5.2	143 ± 5.3	133 ± 5.2	139 ± 5.4
Types of surgery				
– gynaecological	19	16	18	18
– urological	6	9	7	7

Group S=saline infusion + saline injection, Group L=saline infusion + lidocaine (1 $mg \cdot kg^{-1}$) injection, Group PG=prostaglandin E_1 (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion + saline injection, Group PG-L=prostaglandin E_1 (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion + lidocaine (1 $mg \cdot kg^{-1}$) injection. SBP: systolic blood pressure, DBP diastolic blood pressure, HR: heart rate. $P > 0.05$ for all variables.

TABLE II Maximum haemodynamic changes (% mean ± SEM) from levels at the end of surgery (baseline) to levels associated with tracheal extubation, number of patients (n=25 for each group) with increases in BP and HR of > 20% and with cough or strain, and the quality score of tracheal extubation [median (range)].

	Group S	*Group L*	*Group PG*	*Group PG-L*
Maximum Percent Changes (%)				
SBP	38 ± 4	17 ± 2*	9 ± 1*†	8 ± 1*†
DBP	33 ± 3	18 ± 2*	7 ± 1*†	6 ± 1*†
HR	45 ± 4	25 ± 3*†	46 ± 4	31 ± 3*†
Number of Patients				
SBP > 20%	21	12*	1*†	0*†
DBP > 20%	20	12*	0*†	0*†
HR > 20%	24	14*†	25	17*†
Cough/Strain	25	13*†	25	14*†
Extubation Quality Score	3 (2–5)	2 (1–3)*†	3 (2–5)	2 (1–4)*†

Group S=saline infusion + saline injection, Group L=saline infusion + lidocaine (1 $mg \cdot kg^{-1}$) injection, Group PG=prostaglandin E_1 (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion + saline injection, Group PG-L=prostaglandin E_1 (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion + lidocaine (1 $mg \cdot kg^{-1}$) injection. SBP: systolic blood pressure, DBP diastolic blood pressure, HR: heart rate. Extubation Quality Score: 1= no coughing or straining, 2 = very smooth, minimal coughing, 3 = moderate coughing, 4 = high degree of coughing or straining, and 5 = poor extubation, very uncomfortable. *$P < 0.05$ *vs* Group S (control), †$P < 0.05$ *vs* Group L, t $P < 0.05$ *vs* Group PG.

Group S increased markedly in response to tracheal extubation (Figures 1 and 2, Table II).

The increases in SBP and DBP were less in the other three groups. Attenuation of BP increases was greater in Group PG-L than in Groups L and PG. The HR increase was attenuated in Groups L and PG-L but not in Group PG. None of the patients in Group PG-L had BP increases > 20% over baseline (Table II). In this group, the number of patients who experienced > 20% increases in HR was lower than that in either Group S or PG, and similar to that in Group L. Fewer patients experienced coughs or strains in the lidocaine-treated groups than in the groups not treated with lidocaine (Table II). Quality of extubation was better in Groups L and PG-L than in Groups S and PG. No patients in the PGE_1-treated groups developed profound hypotension severe enough to require pressor drugs during tracheal extubation or in the ward. Phlebitis without any subjective symptom developed in 14 and 12 patients in Groups PG and PG-L, respectively, and disappeared within several hours without any pharmacological treatment.

Discussion

The cardiovascular disturbances associated with tracheal extubation are not dangerous in otherwise healthy patients. In contrast, myocardial ischaemia may occur during tracheal extubation in patients with CAD,[7,8] and

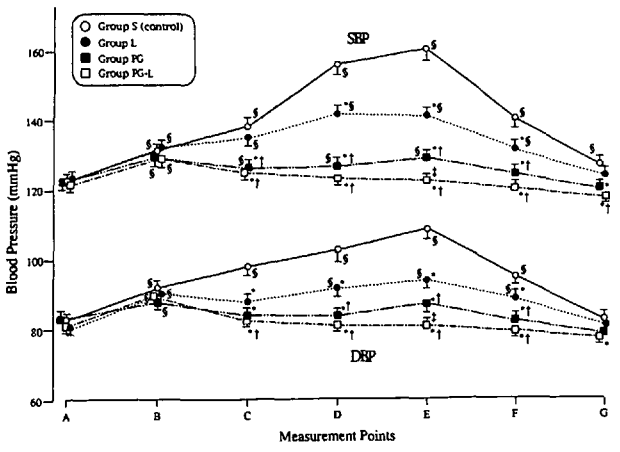

FIGURE 1 Changes in systolic and diastolic blood pressure during emergence from anaesthesia and tracheal extubation (mean ± SEM).

SBP: systolic blood pressure
DBP: diastolic blood pressure
*$P < 0.05$ *vs* control group
†$P < 0.05$ *vs* Group L
‡$P < 0.05$ *vs* Group PG
§$P < 0.05$ *vs* baseline values within groups.

Measurement points; A: start of infusion of PGE_1 or saline, B: administration of lidocaine or saline, C: 1 min before tracheal extubation, D: tracheal extubation, E: 1 min after tracheal extubation, F: 5 min after tracheal extubation, G: 10 min after tracheal extubation.

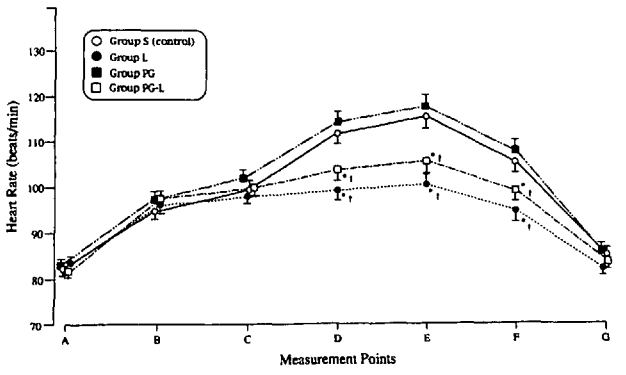

FIGURE 2 Changes in Heart Rate during Emergence from Anaesthesia and Tracheal Extubation (Mean ± SEM).

*$P < 0.05$ *vs* control group
†$P < 0.05$ *vs* Group PG. Heart rate at points B to F were $P < 0.05$ *vs* baseline values within each group in all groups.
Measurement points (A-G) were shown in the legend of Figure 1.

the occurrence of postoperative ischaemia is associated with perioperative myocardial infarction.[9] As HR is a major controllable determinant of myocardial oxygen balance,[10] attenuation of tachycardia by the PGE_1-lidocaine combination may justify concomitant use rather than treatment with PGE_1 alone in this setting. Addition of lidocaine to PGE_1 suppressed coughing and straining during tracheal extubation, providing better quality of extubation. Suppression of tracheal irritation by lidocaine probably contributed to successful attenuation of tachyardic response in the combination method. However, administration of PGE_1 and lidocaine to patients with a decreased ejection fraction and those receiving antihypertensive medication may be associated with adverse consequences. Thus, our technique cannot be applied to this population.

In conclusion, the combination of PGE_1 infusion and lidocaine injection attenuated the haemodynamic responses to tracheal extubation. The anti-hypertensive effect of the combination was superior to that of PGE_1 or lidocaine alone, and the anti-tachycardic effect was similar to that of lidocaine.

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