Treatment of intrathecal morphine-induced pruritus following Caesarean section

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Purpose: To compare both the efficacy and cost of nalbuphine and diphenhydramine in the treatment of intrathecal morphine-induced pruritus following Caesarean section.

Methods: Eighty patients, undergoing elective Caesarean section under spinal anaesthesia, were randomized, in a prospective, double-blind trial, to receive either nalbuphine (Group NAL) or diphenhydramine (Group DIP) for the treatment of SAB morphine-induced pruritus. All patients received an intrathecal injection of 10–12 mg hyperbaric bupivacaine 0.75% and 200 μg preservative free morphine. Postoperative pruritus was assessed, using a visual analogue scale (VAS), for 24 hr. Pruritus treatment was administered upon patient request and by a nurse blinded to the treatment given. Patients who failed to respond to three doses of the study drug were deemed treatment failures. Patient satisfaction was assessed with a questionnaire given 24 to 48 hr after surgery. Direct drug costs were calculated based on the pharmacy provision costs as of April 1996.

Results: Eighty patients were enrolled and 45 requested treatment for pruritus. Patients treated with NAL (n = 24) were more likely to achieve a VAS score of zero with treatment (83% *vs* 43%, $P < 0.01$), had a higher ΔVAS following treatment (4 ± 2 *vs* 2 ± 2, $P < 0.003$), and experienced fewer treatment failures (4% *vs* 29%, $P < 0.04$), than those treated with DIP (n = 21). Group NAL patients were also more likely to rate their pruritus treatment as being good to excellent (96% *vs* 57%, $P < 0.004$). Direct drug costs were higher for NAL than for DIP ($6.4 ± 3.1 *vs* $1.7 ± 0.7, respectively, $P < 0.0001$).

Conclusion: Nalbuphine is more effective than diphenhydramine in relieving pruritus caused by intrathecal morphine and the cost differences are small.

Objectif : Comparer l'efficacité et le coût de la nalbuphine avec ceux de la diphenhydramine administrée après la césarienne comme traitement du prurit provoqué par la morphine sous-arachnoïdienne.

Méthodes : Dans cette étude prospective en double aveugle, 80 parturientes opérées pour une césarienne non urgente sous rachianesthésie ont été réparties au hasard pour recevoir comme traitement du prurit provoqué par la morphine soit de la nalbuphine (groupe NAL), soit de la diphenhydramine (groupe DIP). Toutes les patientes ont reçu une injection sous-arachnoïdienne de 10–12 mg de bupivacaïne 0,75% hyperbare avec 200 μg de morphine sans préservatif. Une échelle visuelle analogique (ÉVA) a servi à évaluer l'intensité du prurit postopératoire pendant 24 h. Le traitement antiprurigineux a été administré à la demande de la patiente et par une infirmière ignorant la nature du traitement. On considérait le traitement comme un échec en l'absence de réponse à trois doses de la drogue étudiée. La satisfaction de la patiente était évaluée avec un questionnaire administré 24 à 48 h après la chirurgie. Les coûts d'approvisionnement de la pharmacie en avril 1996 représentaient les coûts directs des produits utilisés.

Résultats : Quarante-cinq des 80 participantes à l'étude ont demandé un traitement antiprurigineux. Les patientes traitées avec NAL (n=24) avaient plus de chance d'obtenir la cote zéro sur l'ÉVA (83% *vs* 43%, $P < 0,01$), avaient un ΔÉVA plus élevé après traitement (4 ± 2 *vs* 2 ± 2, $P < 0,003$) et ont subi moins d'échecs thérapeutiques (4% *vs* 29%, $P < 0,04$) que celles du groupe DIP (n=21). Le groupe NAL avait une plus forte tendance à juger le traitement antiprurigineux de bon à excellent (96% *vs* 57%, $P < 0,004$). Les coûts directs étaient plus élevés pour NAL que pour DIP (6,4$ ± 3,1 *vs* 1,7$ ± 0,7, $P < 0,0001$).

Conclusion : La nalbuphine soulage plus efficacement le prurit provoqué par la morphine sous-arachnoïdienne que la diphenhydramine et la différence des coûts est minime.

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THE addition of preservative-free morphine to intrathecally injected local anaesthetic provides effective, long-lasting postoperative analgesia following Caesarean section under spinal anaesthesia.[1-2] However, a common side-effect of intrathecal morphine administration has been the development of pruritus, occurring in up to 80% of patients.[3-5] This adverse effect has been treated with a number of medications, including nalbuphine, diphenhydramine, naloxone, and subhypnotic doses of propofol.[6-8] Among these drugs, nalbuphine and diphenhydramine have been used most frequently in our institution. However, there are no studies that compared the efficacy and cost of nalbuphine and diphenhydramine for the treatment of intrathecal morphine-induced pruritus.

To address these issues, a randomized, double-blind study was undertaken to compare the efficacy of nalbuphine with that of diphenhydramine in the treatment of intrathecal morphine-induced pruritus, and to establish the cost of treatment with these two drugs.

Methods

Study population

Following institutional Research Ethics Board approval, 80 patients signed a written informed consent to participate in this study. Inclusion criteria for this prospective, randomized, double-blind, clinical trial included: ASA class I or II; patients scheduled to undergo elective Caesarean section; and patient consent to spinal anesthesia. Exclusion criteria included: contraindications to regional anaesthesia; non-elective surgery; current use of mood altering drugs; and known allergy to any of the study medications. Patients were allocated, according to a computer-generated randomization schedule, to one of two study groups: Group NAL (nalbuphine) or Group DIP (diphenhydramine).

Anaesthetic technique

Patients were hydrated with 25 $ml \cdot kg^{-1}$ warmed normal saline before administration of the subarachnoid anaesthetic, and the block was performed with the patient in the sitting position. Following sterile preparation and draping and skin anaesthesia at either the L_{2-3} or L_{3-4} interspace, the subarachnoid space was located with a 27 gauge Whitacre needle inserted through an 18 gauge introducer needle. Once free flow of clear cerebrospinal fluid had been demonstrated, 10–12 mg hyperbaric bupivacaine 0.75% and 200 μg preservative-free morphine, mixed in the same syringe, were injected over 15 sec. Afterwards, patients were immediately placed in a supine, wedged position, monitors were activated and supplemental oxygen was delivered by nasal prongs at 3 $L \cdot min^{-1}$. The level of sensory block was documented by loss of cold sensation to an alcohol swab, and surgery commenced when the block reached $T_4 \pm 2$ dermatomal levels bilaterally.

Intraoperative hypotension (a 30% decrease in SBP from the pre-block value and/or a SBP < 100 mmHg) was treated with 100–500 ml fluid boluses *iv* and 5–15 mg ephedrine *iv*. Persistent intraoperative nausea, unrelated to hypotension, was treated with 25 dimenhydrinate *iv*, and intraoperative pain was treated with 50 μg fentanyl *iv* administered as needed. Postoperatively, patients were administered 400 mg ibuprofen q6h *po* while they were awake and acetominophen with codeine tablets (Tylenol #3), two tablets every three hours were available, if requested, for breakthrough pain.

Measurements

The level of sensory block and occurrence of intraoperative adverse events, including hypotension, nausea and vomiting, pruritus, and pain were documented. The administration of opioids and/or anti-emetics and the occurrence of pruritus in the post-anaesthetic care area were recorded.

Patients were monitored for 24 hr, according to the institutional monitoring protocol for intrathecal opioid administration which involves assessment of the degree of sedation as well as respiratory status. Patients were assessed, when awake, every hour for 12 hr, then every four hours for a total of 24 hr following subarachnoid anaesthesia. Using the same schedule, the presence of pruritus, nausea and/or vomiting and breakthrough pain requiring analgesia was documented by the patient's nurse through direct questioning. A 10 cm visual analogue scale (VAS) with two anchor points, zero and 10, was used to determine the severity of pruritus.

Assessment and treatment of pruritus and/or nausea and vomiting was carried out by nurses blinded to the patient group allocation and treatment protocol. Treatment was provided only at the patient's request and according to the protocol outlined in Table I. Each treatment dose was premixed in a 50 ml bag of normal saline, and labelled only as being either first, second, or third dose. Each dose was administered over 15 min with subsequent doses being given q30 min if symptoms persisted or recurred. Patients who continued to have pruritus after three doses of the

TABLE I Pruritus Treatment Protocol

Group	*First dose*	*Second dose*	*Third dose*
Nalbuphine	5 mg	10 mg	10 mg
Diphenhydramine	25 mg	50 mg	50 mg

study medication were considered treatment failures, and were treated at the discretion of the attending anaesthetist. Nausea and/or vomiting were treated with 25 mg dimenhydrinate *iv* q4-6 hr *prn* on patient request. Other adverse effects in the perioperative period were recorded.

Patient satisfaction was assessed by conducting a structured, questionnaire-based interview, 24–48 hr postoperatively. During this interview, patients were asked to rate their satisfaction with pruritus treatment and pain management on a four-point scale (excellent, good, fair, poor). They were also asked to rate their overall satisfaction with the quality of care provided, and questioned if they would elect to have the same anaesthetic again.

A cost-benefit comparison of the two study drugs was done by directly comparing drug costs, based on the pharmacy provision cost of each medication as of April 1996.

Statistical analysis

Collected data were analysed using Student t test, Chi-square statistic, and Fisher's Exact test, as appropriate. All statistical analyses were performed using Primer of Biostatistics® software, version 3.01 for IBM PC (McGraw-Hill, Inc.). Data throughout the text and tables are presented as mean ± SD, and statistical significance was assumed when $P < 0.05$.

Results

Patient population and intraoperative course

All patients completed the study protocol, and demographic data were similar in the two treatment groups (Table II). The majority of subjects were ASA class I with a mean patient age of 31.6 yr. None of the patients experienced adverse surgical or anaesthesia-related complications intraoperatively.

TABLE II Demographic Data

Group	*Nalbuphine*	*Diphenhydramine*
n	40	40
Age *(yr)**	31.2 ± 4.4	32.0 ± 3.6
Weight *(kg)**	81.0 ± 14.9	76.3 ± 13.6
Height *(cm)**	163.1 ± 8.1	160.9 ± 6.1
Primigravida *(n)*	5	8
Gestational age *(wk)**	38.2 ± 1.0	38.6 ± 0.9
ASA class *(I/II)*	28/12	35/5
Pruritus *(n)*		
intraoperative	2.5% (1)	7.5% (3)
PACU	62.5% (25)	65.0% (26)
postoperative	90% (36)	90% (36)

*expressed as mean ± SD

Postoperative pruritus

Pruritus occurred intraoperatively in some patients although the majority of patients experienced pruritus after PACU discharge, typically an hour or more after the end of surgery (Table II). Ninety percent of patients in both treatment groups had postoperative pruritus; 66.7% of subjects in group NAL and 58.3% in group DIP requested treatment for this adverse event (Table III). There was no difference in the intensity of pruritus, as measured by VAS, in the patients requesting treatment in the two groups (NAL 5 ± 2, DIP 5 ± 2). The VAS scores for patients not requesting treatment in the two groups were NAL, 2 ± 1 and DIP, 3 ± 2. Patients received an average of two doses for the treatment of pruritus in both study groups. The proportion of patients who achieved a VAS score of zero after treatment for pruritus was higher in group NAL than in group DIP (83% *vs* 43%, $P < 0.01$). In addition, the change in VAS (VAS) following treatment was greater when nalbuphine was administered ($P < 0.003$, Table III). One patient in group NAL and six patients in group DIP failed to respond to the treatment protocol (4% *vs* 29%, $P < 0.04$). All failure of therapy patients were given nalbuphine *iv* rescue treatment with favorable results.

Postoperative adverse events

There was no difference in the proportion of patients in each group who were sedated with anti-pruritic therapy; eight patients reported being sedated, three in group NAL and five in group DIP (Table III). None of these patients had respiratory depression (respiratory rate < 10 per min) nor were they difficult to arouse. Postoperative nausea and/or vomiting was observed in 62.5% of NAL-treated patients and 42.9%

TABLE III Postoperative Pruritus

Group	*Nalbuphine*	*Diphenhydramine*
Treatment requested *(n)*	24	21
Doses per patient *(n)*	2 ± 1	2 ± 1
Sedation with treatment *(n)*	3	5
Pretreatment VAS score	5 ± 2	5 ± 2
Treatment failure *(n)*	1*	6
VAS = 0 after therapy *(n)*	20†	9
ΔVAS	4 ± 2‡	2 ± 2
Direct costs *($)*	6.4 ± 3.1§	1.7 ± 0.7

VAS=visual analogue scale; VAS=change in visual analogue scale score with treatment.

**P < 0.04, different from diphenhydramine group.*

†*P < 0.01, different from diphenhydramine group.*

‡*P < 0.003, different from diphenhydramine group.*

§*P < 0.0001, different from diphenhydramine group.*

of DIP-treated patients (NS, $P = 0.31$) and it tended to occur later than did pruritus. The overall incidence of nausea and/or vomiting among all study patients, including those not treated for pruritus was 62.5%. No patient required supplemental postoperative narcotics for breakthrough pain, and no other adverse events were seen in this study.

Direct drug costs

Treatment of intrathecal morphine-induced pruritus with nalbuphine was associated with higher direct drug costs than with diphenhydramine, with mean cost per patient of \$6.4 ± 3.1 and \$1.7 ± 0.7, respectively ($P < 0.0001$).

Patient satisfaction

A greater proportion of patients in group NAL rated their pruritus treatment as being good to excellent (63% *vs* 33%, $P < 0.004$). Pain relief was described as being good to excellent in all but one patient in both study groups. Nearly all patients were satisfied with the quality of care they received, and they unanimously said they would have the same anaesthetic again with the exception of one patient in group DIP (Table IV). This patient rated her pruritus treatment as being poor but, because we did not explicitly ask for reasons why she would prefer not to have the same anaesthetic again, we do not know the reason for her overall dissatisfaction.

Discussion

We found that nalbuphine was superior to diphenhydramine in the treatment of pruritus caused by intrathecal morphine given for analgesia after Caesarean section. A higher proportion of nalbuphine-treated patients had either greater or total symptom relief and fewer patients experienced treatment failure. There was no evidence that nalbuphine had a deleterious effect on the analgesia. Nor was there evidence that it altered the incidence of nausea compared with either those patients who received diphenhydramine or those who received no treatment for pruritus. Our findings are consistent with those of Cohen[6] who found nalbuphine to be both effective and superior to naloxone in the treatment of pruritus and nausea in Caesarean section patients treated with *epidural* morphine. In contrast to the our findings and those of Cohen, Morgan reported that nalbuphine was ineffective against epidural morphine-induced pruritus following Caesarean section.[9] However, nalbuphine was given routinely to all patients by Morgan whereas, in both our study and that of Cohen, only patients who requested treatment for pruritus were treated. The greater ΔVAS and the higher number of patients achieving total symptom relief with nalbuphine treatment suggests that it may be of particular value in treating patients with severe or intractable pruritus following administration of intrathecal morphine. However, this hypothesis was not specifically tested by our protocol and would need to be further studied.

Cohen[6] observed higher sedation scores in nalbuphine-treated patients than in those who received naloxone. Similarly, we found that 12.5% of nalbuphine treated patients subjectively felt sedated but it was not the uniform finding as in Cohen's report. Two factors may account for the difference in our result. First is the time interval over which the therapeutic interventions were administered. In Cohen's study, 60% of treated patients received two doses of nalbuphine (5 mg each) during the six hour study period, and 20% of subjects required an additional 5 mg in the same period of time. In comparison, patients in our study received 15 ± 5 mg of nalbuphine during the 24 hr study. Second, our assessment was subjective and it is possible that we underestimated the incidence of sedation with nalbuphine treatment by not using a more objective tool. However, sedation was mild and the incidence was no higher than that seen with diphenhydramine.

The most common side effect of intrathecal opioid administration is pruritus, typically localized to the face, neck, or upper thorax and usually occurring within a few hours of injection.[10] The incidence varies widely but it occurs commonly in obstetric patients. Pruritus induced by intrathecal opioid administration is likely due to cephalad migration of the drug in cerebrospinal fluid and subsequent interaction with opioid receptors in the central nervous system. Nausea and vomiting are also common following intrathecal injection of opioids. Nausea usually occurs within four

TABLE IV Patient satisfaction

Group	*Nalbuphine*	*Diphenhydramine*
Pruritus therapy *(n)*		
Excellent/Good	23*	12
Poor/Fair	1*	9
Pain relief *(n)*		
Excellent/Good	39	39
Poor/Fair	1	1
Overall satisfaction *(n)*		
Excellent/Good	39	39
Poor/Fair	1	1
Would have the same anaesthetic again *(n)*	40	39

*$P < 0.004$, different from diphenhydramine group.

hours of injection and vomiting soon thereafter.[11] Nausea and vomiting induced by intrathecal opioids also result from the cephalad migration of drug in cerebrospinal fluid and subsequent interaction with opioid receptors located in the central nervous system. Sensitization of the vestibular system to motion produced by opioids may also play a role in the nausea and vomiting induced by intrathecal opioids.[12]

Treatment of the side effects of epidural and intrathecal opioids was initially focused on the prevention and treatment of respiratory depression. Both naloxone, a pure antagonist, and mixed agonist-antagonists were used and found to be effective. However, naloxone use was associated with reversal of analgesia and its administration for the treatment of the non-threatening side-effects of intraspinal opioids is not encouraged.[6,13] Nalbuphine, a mixed antagonist-agonist is an antagonist at the μ receptor, and reverses the respiratory depression caused by intravenous, epidural and intrathecal administration of opioids. It is a weak agonist at the κ opioid receptor, resulting in analgesia and sedation and at the σ receptor, occasionally producing dysphoria, confusion and hallucinations. Nalbuphine is as effective as naloxone for the treatment of respiratory depression and more effective for the treatment of nausea and pruritus caused by epidural morphine. Reversal of epidural morphine analgesia by nalbuphine has not been described in either obstetric or non-obstetric patients treated with epidural morphine and our findings are consistent with this.[6,14,15] There is a case report describing improved analgesia and reversal of side effects by nalbuphine in a patient who had received epidural morphine after cesarean section.[16]

Although opioids may liberate histamine from mast cells, this does not appear to be the mechanism underlying pruritus after intrathecal opioids. However, antihistamines may be an effective treatment for pruritus, likely secondary to their sedative effects and they are used widely for this indication. Whether they are preferable to using nalbuphine to treat the common side effects of intrathecal morphine had not been previously studied and our data suggest that they are not. We did not find a difference in the incidence of nausea and vomiting in patients treated for pruritus, either when we compared them with untreated patients, or when we compared the two treatment groups. However, if we expanded our study population to 40 treated patients in each group, the incidence in DIP-treated patients (42.9%) would have been significantly lower than that in the NAL treated patients (62.5%). We acknowledge the potential for a type 2 error and regard this as important in that the difference, if real, would be of sufficient magnitude to be clinically important. Diphenhydramine may be more effective than nalbuphine in the treatment of nausea even though the converse is true for pruritus and this may be related to the underlying aetiology of the adverse effects. The pruritus is predominantly a central opioid effect, thus making nalbuphine the logical choice for reversal. However, nausea and vomiting after intrapelvic surgery results from a number of causative factors and may respond more favourably to treatment with anti-emetic agents. It may be that therapy for adverse effects attributed to intrathecal narcotics should be selective and directed at the specific adverse effect experienced.

A pharmaco-economic appraisal is a necessary part of the assessment of any new therapeutic strategy. Our costing analysis indicated that the direct drug costs were higher with nalbuphine therapy than with diphenhydramine. However, drug costs *per se* were trivial and the observed differences in cost should not support avoidance of nalbuphine therapy. Additional costs that should be considered are the labour (nursing) costs of managing patients with adverse effects. The higher failure rate with diphenhydramine increased the number of nursing interventions and would have increased this component of costs. Unfortunately, we did not quantify labour costs. The higher patient satisfaction observed amongst nalbuphine-treated patients, when combined with its greater effectiveness in relieving pruritus, easily justifies the increased costs associated with nalbuphine administration.

In conclusion, we found that nalbuphine was superior to diphenhydramine for the treatment of pruritus caused by subarachnoid morphine given during Caesarean section and its use is associated with a higher degree of patient satisfaction. There is a minor cost increment with the use of nalbuphine than with the use of diphenhydramine for this indication, but this increment is easily justified given the patient response to treatment. Finally, nalbuphine may be more efficacious in alleviating the more severe or intractable forms of pruritus resulting from subarachnoid morphine and this deserves further study.

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SEVOFLURANE has certain properties, such as a pleasant odour, little irritation of the airways, and a low blood gas partition coefficient, that favour rapid inhalation induction.[1] Therefore, sevoflurane appears to be useful for the induction of anaesthesia. Rapid inhalation induction with a maximal inspiratory effort (the single vital capacity breath method) using a high concentration of sevoflurane is acceptable to patients and reduces the induction time compared with the conventional inhalation method[2] in which a low concentration of anaesthetic is given initially and increased gradually. However, the single vital capacity breath method requires cooperation of the patient.

As an alternative to the vital capacity method, we have previously reported the haemodynamic effects associated with rapid induction using sevoflurane 7% inhalation with tidal volume breathing,[3] which does not require cooperation of the patient. However, the changes of plasma catecholamine concentrations have not been determined by this method. Therefore, in this study, we compared the haemodynamic and plasma catecholamine changes associated with induction of anaesthesia using tidal volume or slow inhalational breathing of sevoflurane, and rapid intravenous induction using thiamylal.

Materials and methods

Subjects

After obtaining approval from the Institutional Ethics Committee and informed consent, 24 patients (age: 37 to 68 yr; ASA class: 1 or 2) scheduled to undergo elective surgery were studied. They were divided into three groups of eight patients each at random using an envelope method. All patients were given 0.5 mg atropine and 0.05 $mg \cdot kg^{-1}$ midazolam *im* 15 min before entering the operating room.

Anaesthesia induction

All patients received 100% oxygen for several minutes prior to induction then 1 mg vecuronium as a priming. Immediately after vecuronium, induction was commenced as follows. In Group A, anaesthesia was induced with inhalation of sevoflurane 7% (inspiratory concentration) for three minutes[3] using a vaporizer (PPV Sigma 7%, Penlon, Abingdon UK). For Group B induction involved inhalation of increasing sevoflurane concentration (inspiratory) rising by 0.5% every two or three breaths up to 5% and then maintaining 5% for seven minutes (conventional slow induction method).[3] Group C received 5 $mg \cdot kg^{-1}$ thiamylal (control group). From the start of induction, patients in groups A and B received nitrous oxide (3 $l \cdot min^{-1}$) in oxygen (3 $l \cdot min^{-1}$) and those in Group C received oxygen (6 $l \cdot min^{-1}$). Tracheal intubation was facilitated, in all patients, with 0.15 $mg \cdot kg^{-1}$ vecuronium *iv* (including priming dose of 1 mg), the remainder of the dose was administered when patients lost their verbal response. Intubation was performed, by the same anaesthetist, when train of four response at the thumb had disappeared. Following intubation, patients in all groups received sevoflurane 0.5% with nitrous oxide (3 $l \cdot min^{-1}$) in oxygen (2 $l \cdot min^{-1}$). No surgical stimulation was performed until the end of the study. After intubation, ventilation was controlled to maintain $P_{ET}CO_2$ (Ultima™, Datex, Finland) between 32 and 38 mmHg.

Measurements

Blood pressure, heart rate and plasma epinephrine and norepinephrine concentrations were measured just before the start of induction, immediately before intubation and at 1 (haemodynamics only), 3, 5 and 10 min after intubation. Rate pressure product was calculated using systolic blood pressure and heart rate. Before induction, a radial artery was cannulated to collect blood samples for determination of catecholamines and to measure blood pressure. Heart rate was measured by ECG and rate pressure product was calculated. The blood samples were centrifuged and plasma was frozen at –20°C until assay. Plasma epinephrine and norepinephrine concentrations were measured by high-performance liquid chromatography (NT detector, Yokohama Hewlett-Packard, Yokohama, Japan; detection limit 0.01 $ng \cdot ml^{-1}$, coefficient of variation of 3.1% for epinephrine and 2.7% for norepinephrine). End-tidal sevoflurane concentrations (S_{ET}) were measured using Ultima™ (Datex, Helsinki, Finland).

Data analysis

Demographic data were compared among the three groups using the chi-square test or the Kruskall Wallis test. End-tidal sevoflurane concentration, blood pressure, heart rate, rate pressure product, and plasma catecholamine concentrations were compared using analysis of variance (ANOVA) followed by Scheffe's test. Intragroup changes were also compared using the ANOVA with repeated measures followed by Scheffe's test. A P value < 0.05 was considered statistically significant.

Results

The demographic data, duration of anaesthesia, and duration of surgery were not different among the three groups (Table I).

End-tidal sevoflurane concentration in Group A (sevoflurane 7%) was higher than in Group B (slow induction) before intubation, but there were no differences between the two inhalation groups after intubation (Figure 1).

TABLE I Demographic data

Group	*A*	*B*	*C*
Age (yr)	61 ± 4	59 ± 3	61 ± 3
Sex (Male/Female)	4/4	5/3	5/3
Weight (kg)	55.4 ± 2.0	56.3 ± 2.6	53.8 ± 2.7
Duration of			
Surgery (min)	230 ± 36	235 ± 31	228 ± 30
Anaesthesia (min)	318 ± 42	313 ± 36	313 ± 34

mean ± SEM

A: 3-min inhalation of sevoflurane 7%

B: 7-min inhalation of sevoflurane 5%

C: thiamylal (5 mg·kg^{-1} *iv*)

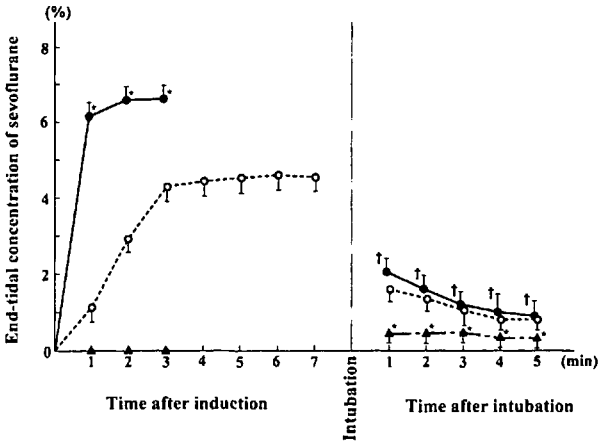

FIGURE 1 End-tidal concentration of sevoflurane during induction of anaesthesia Closed circles Group A (three minutes sevoflurane 7%), open circles Group B (seven minutes sevoflurane 5%, slow induction), closed triangles Group C (thiamylal).

Mean ± SEM. n=8.

*$P < 0.05$ *vs* Group B. †$P < 0.05$ *vs* Group C.

Haemodynamic variables

Blood pressure increased in Group C (thiamylal) after induction (mean blood pressure: from 95 ± 5 mmHg to 111 ± 5 mmHg, mean ± SEM) as well as after intubation (to 133 ± 5 mmHg). In contrast, blood pressure did not increase in groups A and B. The decrease of blood pressure after induction in Group A (2 ± 1 mmHg) was less than in Group B (10 ± 2 mmHg).

Heart rate increased in all groups after induction, but there were no differences among groups.

Rate pressure product at one minute after intubation in Group C was higher than in the inhalation induction groups (Figure 2).

Plasma catecholamines

Plasma epinephrine concentrations decreased in all three groups and there were no differences among them. However, norepinephrine concentrations increased before and after intubation in groups A and B. In Group C, no increase in norepinephrine concentration was seen before intubation, but the concentration increased after intubation (Figure 3).

Discussion

Rapid induction with sevoflurane 7% inhalation and tidal volume breathing induced the least change in blood pressure. Plasma catecholamine concentrations after induction were similar in the two inhalation groups, i.e., plasma epinephrine decreased while norepinephrine increased.

Similar divergent changes in catecholamine concentrations as shown in the present study have been reported previously and were attributed to different effects on the baroreceptor and sympathetic systems.[4] These differences may be related to the sources of plasma epinephrine and norepinephrine. Epinephrine is mainly released from the adrenal medulla,[5] whereas norepinephrine is derived from the sympathetic nervous system. It has been demonstrated that norepinephrine may be more reliable for assessing sympathetic activity, because of its short half-life.[6]

The increases in heart rate and plasma norepinephrine concentration before intubation in the inhalation induction groups may have been a sympathetic response to the vasodilatory effect of sevoflurane.[7] Sevoflurane reduces blood pressure without blocking sympathetic activity,[8] likely by a direct effect on baroreceptors. However, isoflurane has recently been reported to produce a dose dependent sympathetic activation in anaesthetized rabbits, but this activation was not mediated via a baroreceptor reflex.[9] Thus, further examination of the mechanisms of action for sevoflurane and isoflurane is required.

In the thiamylal group, plasma norepinephrine concentration did not increase before intubation even though rate pressure product increased. This may reflect a transient sympathetic depression by thiamylal that dose not affect baroreflexes.[10,11]

There are several reports[2,12] regarding haemodynamic changes during the single vital capacity induction method using sevoflurane 7%. A decrease in systolic blood pressure before intubation has been reported which ranges from 21 to 24 mmHg. However, heart rate does not increase,[2,12] indicating that the heart rate response to changing blood pressure was depressed. In contrast, in the present study, inhalation of sevoflurane 7% with tidal volume breathing produced, before intubation, only a slight (6 ± 2 mmHg) decrease in systolic blood pressure which did not differ from pre-induction levels. However, heart rate increased before intubation

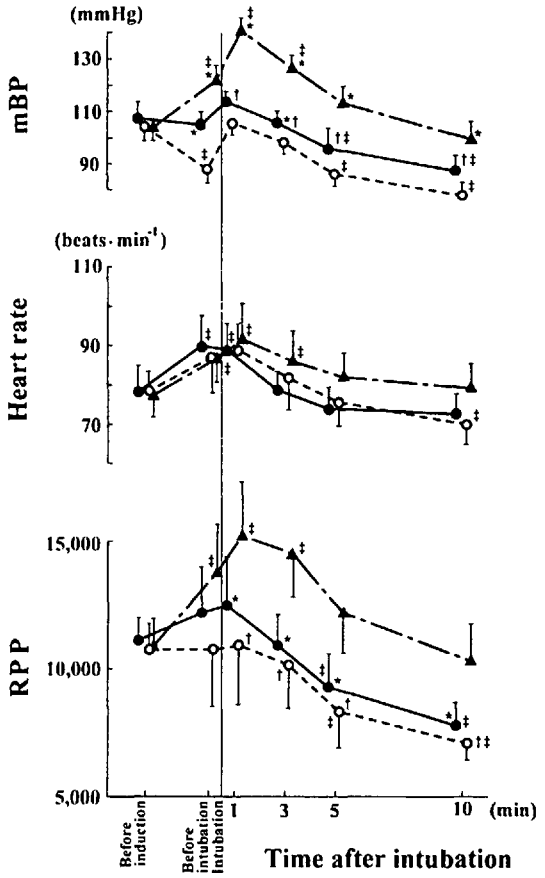

FIGURE 2 Blood pressure, heart rate and rate pressure product during induction of anaesthesia Closed circles Group A (three minutes sevoflurane 7%), open circles Group B (seven minutes sevoflurane 5%, slow induction), closed triangles Group C (thiamylal).

Mean ± SEM. n=8.
*$P < 0.05$ *vs* Group B. †$P < 0.05$ *vs* Group C. ‡$P < 0.05$ *vs* pre-induction value in the same group.
mBP: mean blood pressure, RPP: rate pressure product

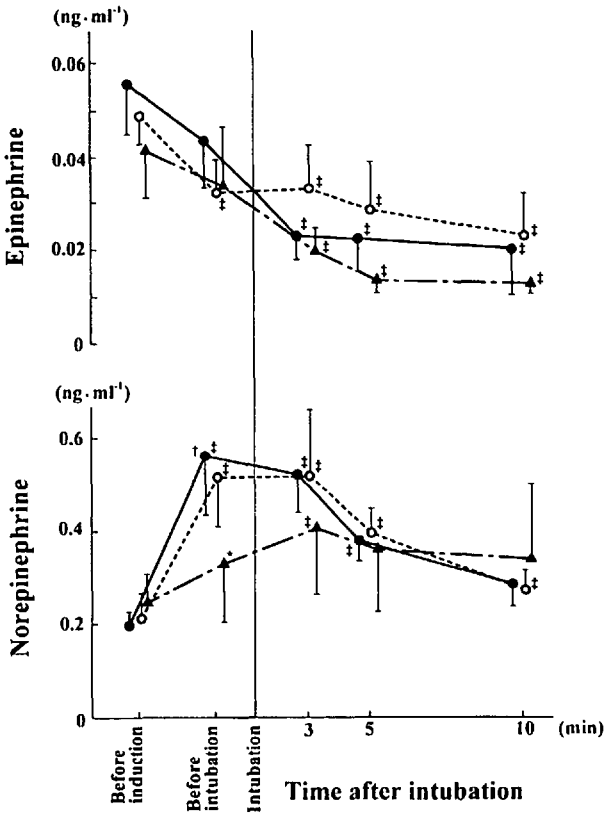

FIGURE 3 Plasma concentrations of catecholamines. Closed circles Group A (three minutes sevoflurane 7%), open circles Group B (seven minutes sevoflurane 5%, slow induction), closed triangles Group C (thiamylal).

Mean ± SEM. n=8. *$P < 0.05$ *vs* Group B. †$P < 0.05$ *vs* Group C. ‡$P < 0.05$ *vs* pre-induction value in the same group.

suggesting that baroreflex function remained intact or was intensified. To our knowledge, there have been no studies regarding the changes in catecholamine concentrations during induction by the single vital capacity breath method with sevoflurane. Therefore, it is difficult to compare the present data with those of the vital capacity method. Further studies are needed to examine more precisely the effects of these different techniques on haemodynamic variables and on the sympathetic nervous system.

In conclusion, one benefit of sevoflurane 7% induction with tidal volume inhalation for three minutes is the absence of blood pressure changes prior to intubation. An additional advantage of tidal volume sevoflurane 7% over thiamylal induction is the avoidance of changes in blood pressure and rate pressure product after intubation. This method could be included as one of the anaesthesia induction techniques using sevoflurane.

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