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Single vital capacity inhalational anaesthetic induction in adults – isoflurane *vs* sevoflurane

Purpose: To evaluate whether isoflurane is as suitable as sevoflurane for the single vital capacity breath (VCB) method of inhalational induction in patients premedicated with midazolam.

Methods: A randomised, controlled, double-blind study involving 67 ASA I-II patients aged between 18-50 yr undergoing elective surgery under general anaesthesia. All participants received premedication with 0.03 mg·kg⁻¹ midazolam iv. Using a primed circle absorber circuit, inhalational induction of anaesthesia was performed with the single VCB method using either isoflurane 3.5% or sevoflurane 7.5% in nitrous oxide 67% in oxygen, representing approximately equivalent MAC-multiples of 3.6 MAC. Isoflurane was compared with sevoflurane in terms of rapidity, efficacy, safety and acceptability of induction.

Results: With the single VCB method, sevoflurane produced a faster (45 ± 21 vs 71 ± 22 sec, $P < 0.01$), more successful (100% vs 75.8%, $P < 0.01$) induction of anaesthesia, with fewer induction-related complications (11.8% vs 84.8%, $P < 0.01$) than did isoflurane. There was also greater patient acceptability of induction with sevoflurane (76.4% vs 42.4%, $P < 0.05$).

Conclusion: In adults given midazolam premedication, isoflurane is not as suitable as sevoflurane for single VCB inhalational anaesthetic induction technique as it is associated with slower, more complicated induction and less patient acceptability.

Objectif : Vérifier si l'isoflurane est aussi approprié que le sévoflurane quand on utilise la méthode de l'inspiration à capacité vitale unique (ICVU) chez des patients qui ont reçu une prémédication de midazolam.

Méthode : Il s'agit d'une étude randomisée, contrôlée et en double aveugle auprès de 67 patients ASA I-II, âgés de 18 à 50 ans, devant subir une chirurgie électorale sous anesthésie générale. Tous les participants ont reçu une prémédication de 0,03 mg·kg⁻¹ de midazolam iv. En utilisant un circuit cercle déjà saturé d'agent, l'induction de l'anesthésie par inhalation a été réalisée selon la méthode de l'ICVU soit avec de l'isoflurane 3,5 %, soit avec du sévoflurane 7,5 % dans un mélange de protoxyde d'azote à 67 % et d'oxygène, ce qui représente environ 3,6 MAC. L'isoflurane a été comparé au sévoflurane en ce qui a trait à la rapidité, l'efficacité, la sécurité et l'acceptabilité de l'induction.

Résultats : Selon la méthode de l'ICVU, le sévoflurane a produit une induction anesthésique plus rapide (45 ± 21 vs 71 ± 22 s, $P < 0,01$) mieux réussie (100 % vs 75,8 %, $P < 0,01$), présentant moins de complications reliées à l'induction qu'avec l'isoflurane (11,8 % vs 84,8 %, $P < 0,01$). Il y a eu également une plus grande acceptabilité des patients pour l'induction avec le sévoflurane (76,4 % vs 42,4 %, $P < 0,05$).

Conclusion : Chez les adultes à qui on administre une prémédication de midazolam, l'isoflurane n'est pas aussi approprié que le sévoflurane lors de l'utilisation de la technique de l'ICVU parce qu'il est associé à une induction plus lente, à des complications plus nombreuses et à une plus faible acceptabilité des patients.

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THE recent introduction of newer inhalational anaesthetic agents has made inhalational induction of anaesthesia a more attractive alternative to intravenous induction for adults.¹ Inhalational induction allows the use of a single agent for both induction and maintenance. The single vital capacity breath (VCB) method is a good method of inhalational induction of anaesthesia and has been used successfully with several inhalational agents, such as cyclopropane,² halothane,³ enflurane,⁴ isoflurane,⁵⁻⁶ and more recently sevoflurane.^{1,7} When compared with the traditional tidal breathing method, this method is faster, more pleasant and produces fewer complications.⁸

Recently, sevoflurane has emerged as the most promising agent for the single VCB method of inhalational induction.^{1,7} However, concern about its relatively high cost has restricted its use. Although isoflurane is much cheaper, it is unpopular due to the reportedly high incidence of complications and the pungency of its vapour.⁹ However, these findings contradict Loper *et al.*, who had demonstrated that the single VCB method utilizing isoflurane was rapid, reliable, and highly acceptable.⁶ This difference may have been due to the use of premedication by the latter study, and its omission in the former.

Therefore, this study aimed at evaluating whether isoflurane was as suitable as sevoflurane for anaesthesia induction with the single VCB method for patients premedicated with midazolam. It compared isoflurane with sevoflurane in terms of rapidity of effect, efficacy, safety, and acceptability of induction.

Methods

After obtaining institutional approval for the study, 67 ASA I & II patients aged between 18 and 50 yr undergoing elective surgery under general anaesthesia with spontaneous respiration were recruited. Exclusions included known allergy or sensitivity to halogenated inhalational agents, known or suspected genetic susceptibility to malignant hyperthermia, history of liver disease, heavy smokers (>20 day⁻¹), and patients with an impaired ability to communicate. The patients were seen preoperatively, where written informed consent was taken, and they were taught the VCB technique. Patients received premedication with 0.03 mg·kg⁻¹ midazolam 15 min before surgery. All patients had intravenous access, which was heparinised and plugged.

The patients were randomized into two groups by computer generated numbers. Group S received sevoflurane 7.5% and group I isoflurane 3.5% in nitrous oxide 67% in oxygen. A circle CO₂ absorber system anaesthetic machine (Narkomed® 4, North American Dräger, USA), was primed by occluding the patient end

and flushing the circuit with the appropriate anaesthetic in a mixture of 4 L·min⁻¹ nitrous oxide and 2 L·min⁻¹ oxygen, with the adjustable pressure limiting (APL) valve fully open, for four minutes. This allowed the inhaled anaesthetic concentration during the vital capacity breath to approximate the dial concentration. The reservoir bag was replaced with two two-litre reservoir bags joined with a Y-piece to ensure that the reservoir was adequate for the vital capacity breath.

Prior to anaesthesia induction, the patients were reminded of the single vital capacity breath method. They were then asked to take a deep breath and then to breathe out to residual volume. The mask attached to the primed circuit was applied firmly to their faces, and they were instructed to take a vital capacity breath and to hold it for as long as possible. If they were unable to maintain the breath-hold, they were encouraged to continue to breathe normally. Anaesthetic gas administration was continued for five minutes before reduction to maintenance concentrations.

Standard monitoring including non-invasive blood pressure, electrocardiogram (lead II), pulse oximetry, end-tidal CO₂ monitoring, end-tidal inhalational agent monitoring, and FiO₂, were instituted and recordings taken every minute for five minutes from the start of induction. The monitors were incorporated onto the anaesthetic machine.

The time of vital capacity breath-hold was taken as the time from achievement to release of the vital capacity breath. Time to loss of consciousness (LOC) was the time from achievement of the vital capacity breath, to failure to obey the verbal command to open their eyes. Patients were asked to open their eyes at 10-sec intervals. An independent, blinded observer noted the presence or absence of complications. These include failure of induction (unable to perform VCB or rescue therapy given), excitatory movements (movement of any limb), coughing, desaturation (pulse oximetry < 90%), apnoea (> 30 sec after completion of the vital capacity breath-hold), excessive secretions (visible secretions around the mask), and laryngospasm. Rescue therapy consisting of 1 mg·kg⁻¹ propofol *iv* and 25 mg succinylcholine *iv* was given if the patient desaturation occurred or if clinically indicated.

Once the patients were orientated and ready for discharge from the post-operative recovery area, they were interviewed as to the smell of the anaesthetic (pleasant, unpleasant, undecided) and whether they were willing to undergo a similar induction (yes, no, undecided). If they had had a previous general anaesthetic, they were asked how this compared with their previous induction (better, worse, no difference).

All results are expressed as mean ± SD. Student's *t* test was used for the patients' variables, duration of

VCB and time to LOC. Repeated measures ANOVA and Bonferroni post-hoc test were used to assess haemodynamic changes. Chi-squared tests, incorporating Fisher's exact test where appropriate, were used for the variables of complications and post-operative assessment. A *P* value of < 0.05 was taken as statistically significant.

Results

Both groups were similar with regards to age, sex, ASA status, weight, number of smokers, and those who had previous general anaesthesia (Table I). Sevoflurane produced more rapid loss of consciousness than isoflurane (Table II). The mean induction times were 45 ± 21 sec for group S and 71 ± 22 sec for group I ($P < 0.01$). The duration of breath-hold was longer in group S (51 ± 20 sec) than in group I (35 ± 19 sec) ($P < 0.01$) (Table II). The mean end-tidal concentrations of the inhalational agents after completion of the VCB were 5.2% for sevoflurane and 2.5% for isoflurane, equivalent to 2.76 MAC and 2.64 MAC respectively ($P > 0.05$).

There were fewer patients with complicated induction using sevoflurane ($n = 4$) than with isoflurane (n

$= 28$) ($P < 0.01$). The four patients in group S had mild complications: Three had a single cough, two of whom moved their arms and one had visible saliva around his mask. The fourth patient was a 25-yr-old woman who had a smooth induction, holding VCB for 50 sec with LOC at 30 sec, but became apnoeic for 90 sec before resuming respiration. Her saturation remained >97% throughout induction. In all patients of group S, anaesthesia was successfully induced.

Most of the induction-related complications of group I were minor and did not interfere materially with induction. The majority were either involuntary movement or coughing. However, coughing led to laryngospasm in seven patients, excessive secretions in five, and oxygen desaturation in four. Of these, in eight patients inhalational induction was unsuccessful (Table II). Six of these patients were rescued with propofol and succinylcholine as required by protocol. These patients included four patients whose pulse oximetry readings decreased to between 79-89%, one patient who sat up due to uncontrolled coughing, and another who developed laryngospasm associated with involuntary movement requiring restraint. The remaining two patients were unable to take a vital capacity breath, and anaesthesia was induced successfully with the tidal breathing method. The data from all eight patients were included in the analysis of all data except for the time of LOC as they did not achieve LOC as defined in the study, and in the haemodynamic changes due to the confounding influence of the administered propofol.

Pre-induction blood pressures and heart rates were similar in both groups. The decrease in systolic and diastolic pressure compared with the preinduction reading was greater in group S, maximal at three minutes after induction. Patients in Group I exhibited an increase in heart rate compared with the preinduction rate, maximal at four minutes after induction (Table III).

Although only 35.3% of the patients found sevoflurane to have a pleasant smell, this was more than with isoflurane (3.0%) ($P < 0.05$). Most patients were willing to undergo a similar induction with sevoflurane (76.4%), compared with 42.4% with isoflurane ($P < 0.05$). Patients who had had a previous intravenous induction found no difference between intravenous and inhalational induction with either isoflurane or sevoflurane (Table IV).

Discussion

This study demonstrates that the single VCB method using isoflurane is unsuitable for anaesthetic induction in adult patients premedicated only with midazolam. There was a high rate of complications for isoflurane (84.8%), which led to failure of induction in 24.2% of

TABLE I Demographic data.

	Group S sevoflurane	Group I isoflurane	
n	34	33	
age (yr)	29 ± 7	31 ± 9	ns
sex (M/F)	17/17	20/13	ns
weight (kg)	65 ± 16	61 ± 14	ns
ASA I/II (n)	28/6	32/1	ns
smokers (n)	3	6	ns
previous GA (n)	13	16	ns

ns: not significant ($P > 0.05$)

TABLE II Results

	Group S sevoflurane	Group I isoflurane	
n	34	33	
Time to LOC (sec)	45 ± 21	71 ± 22 ($n = 25$)	$P < 0.01$
Duration of breath-hold (sec)	51 ± 20	35 ± 19	$P < 0.01$
Number of patients with complications % (n)	11.8 (4)	84.8 (28)	$P < 0.01$
Failure of induction % (n)	0 (0)	24.2 (8)	$P < 0.01$
Involuntary movement % (n)	5.9 (2)	54.5 (18)	$P < 0.01$
Cough % (n)	8.8 (3)	42.4 (14)	$P < 0.01$
Desaturation % (n)	0 (0)	12.1 (4)	ns
Apnoea % (n)	2.9 (1)	0 (0)	ns
Excessive secretion % (n)	2.9 (1)	15.2 (5)	ns
Laryngospasm % (n)	0 (0)	21.2 (7)	$P < 0.01$

ns: not significant ($P > 0.05$)

TABLE III Haemodynamic parameters

	Time after start of induction (min)					
	0	1	2	3	4	5
Group S (n = 34)						
End-tidal sevoflurane (%)		5.2 ± 1.2	5.4 ± 0.7	5.6 ± 0.5	5.7 ± 0.5	5.7 ± 0.5
Systolic pressure (mmHg)	125 ± 14	116 ± 16	106 ± 15	100 ± 16*	101 ± 19	102 ± 20
Diastolic pressure (mmHg)	70 ± 8	66 ± 11	56 ± 11	51 ± 12*	53 ± 14	55 ± 16
Heart rate (beats per minute)	78 ± 12	80 ± 12	81 ± 14	82 ± 14	83 ± 20	81 ± 21
Group I (n = 25)						
End-tidal isoflurane (%)		2.4 ± 0.9	2.7 ± 0.7	2.8 ± 0.6	2.7 ± 0.6	2.7 ± 0.5
Systolic pressure (mmHg)	129 ± 13	131 ± 15	126 ± 15	123 ± 17	129 ± 22	127 ± 24
Diastolic pressure (mmHg)	71 ± 8	73 ± 11	70 ± 13	68 ± 15	68 ± 17	67 ± 21
Heart rate (beats per minute)	76 ± 14	81 ± 15	86 ± 16	94 ± 17	100 ± 20*	97 ± 21

*: $P < 0.05$ [compared to preinduction control (time = 0 min)]

TABLE IV Post-operative interview

	Group S sevoflurane	Group I isoflurane	
<i>Smell</i>			$P < 0.05$
pleasant % (n)	35.3 (12)	3.0 (1)	
unpleasant % (n)	41.2 (14)	45.5 (15)	
undecided/cannot remember % (n)	23.5 (8)	48.5 (16)	
<i>Willingness to undergo similar induction again</i>			$P < 0.05$
yes % (n)	76.4 (26)	42.4 (14)	
no % (n)	11.8 (4)	33.3 (11)	
undecided % (n)	11.8 (4)	22.3 (8)	
<i>Compared to previous GA</i>			ns
better % (n)	15.4 (2)	25.0 (4)	
worse % (n)	23.1 (3)	31.3 (5)	
same / cannot remember % (n)	61.5 (8)	43.7 (7)	

ns: not significant ($P > 0.05$)

the patients. In contrast, in all patients receiving sevoflurane anaesthesia was successfully induced. The mean induction time with sevoflurane was 45 sec, rapid enough to be a viable alternative to intravenous induction. There were no major complications with sevoflurane although there were four patients with minor complications, and only 11.3% of patients were unwilling to undergo a similar induction again.

The use of isoflurane for inhalational induction of anaesthesia defies conventional wisdom, given its pungent odour and propensity for airway irritation. However, with the single VCB method, isoflurane proved to be a reliable, rapid, complication-free and acceptable agent that is superior to halothane.⁵⁻⁶ This suggests that pungency and airway irritation might be of less consequence with the single VCB method than with the traditional tidal breathing method. This may be due to the second gas effect during the breath-hold, which

allows the patient to bypass the excitatory phase.¹⁰

However, a study of the single VCB method in unpremedicated volunteers not only compared sevoflurane favourably with isoflurane, but also associated isoflurane with a high rate of complications.⁹ The earlier success of the single VCB method with isoflurane was achieved with a premedication regimen of fentanyl and glycopyrrolate.⁵ This premedication regimen, through its airway reflex suppression, drying of secretions, sedative, and MAC-reducing effects, may have accounted for the success. In this study, we chose midazolam as it is the most commonly prescribed premedicant in clinical practice. Midazolam has the beneficial effects of anxiolysis, sedation, amnesia, and reducing MAC but lack airway reflex suppression.¹¹ Intravenous midazolam was given in order to standardise the premedication dose on a $\text{mg}\cdot\text{kg}^{-1}$ basis and to eliminate variation in bioavailability from oral or intramuscular dosing. A dose of $0.03 \text{ mg}\cdot\text{kg}^{-1}$ was chosen to ensure that the total dose does not exceed 2.5 mg, the maximum intravenous bolus dose recommended.¹²

Sloan *et al.* compared the single VCB method between sevoflurane and isoflurane in patients premedicated with midazolam.¹³ They showed comparable anaesthesia induction times and high complication rates (isoflurane 92% *vs* sevoflurane 56%) for both groups. However, the authors counted complications that were readily treated by manipulation of the patient's natural airway. The authors also noted that the drawback of their study was the different MAC values of the agents used (sevoflurane 2.9 MAC, isoflurane 4.3 MAC). In addition, they used doses of midazolam which differed by as much as 300% ($0.01\text{--}0.03 \text{ mg}\cdot\text{kg}^{-1}$), and had patients as young as 18 and as old as 87.

We used a narrower age band of 18-50 as the MAC of sevoflurane falls rapidly with increasing age. Sevoflurane in oxygen has a MAC value of 2.6% at age

25, decreasing to 2.1% at age 40, and 1.7% at age 60.¹⁴ Although the MAC value of isoflurane is relatively stable with increasing age, it decreases from 1.28% at age 26 to 1.15% at age 44.¹⁵ Therefore, isoflurane 3.5% and sevoflurane 7.5% would give both groups, who have a mean age of 30 yr, approximately the same MAC-multiple in oxygen. These are also the concentrations used successfully in previous studies.^{5,8} By interpolation, the patients in group I received 2.86 MAC while group S received 3.07 MAC. The addition of nitrous oxide 67% would increase the MAC-multiples of both groups by approximately 0.64 MAC. However, the end-tidal concentrations were not different in MAC terms after the VCB, and during the five-minute monitoring period.

Whilst there has been criticism of past studies comparing different MAC values of inhalational agents during induction,¹⁶ the contribution of MAC is difficult to ascertain. Blood-gas solubility coefficient and inspired agent concentration determine the alveolar concentration of vapour, and may be more important factors than MAC which merely compares anaesthetic potency. Furthermore, MAC refers to a state of equilibrium and certainly, equilibrium is not attained during the single VCB induction. This may have skewed this study, and others using equivalent-MAC comparisons, in favour of the agent with the lower blood-gas solubility coefficient, namely sevoflurane.

An area of concern is the greater decrease in systolic (125 to 100 mmHg) and diastolic (70 to 51 mmHg) blood pressures from preinduction levels in the sevoflurane group. This could be attributed to the slightly greater end-tidal MAC-multiples of sevoflurane achieved, although this did not reach statistical significance. Another reason could be the more rapid attainment of surgical anaesthesia in the sevoflurane patients. Although the decreases were not clinically important in the young ASA I and II patients studied, it implies that the VCB method when combined with high MAC multiples of sevoflurane may be unsuitable for patients with unstable haemodynamics.

Our patients found that sevoflurane had a more pleasant smell and provided a more acceptable induction of anaesthesia than isoflurane. However, it was surprising that slightly more patients found the smell of sevoflurane to be unpleasant than pleasant contrary to published data.¹⁷ This difference may be due to our use of midazolam, which may have introduced a bias to the post-operative interview as some of the patients were unable to recall the induction at all. It is therefore difficult to interpret the significance of this data.

In conclusion, in adults given midazolam premedication alone, isoflurane was not as suitable as sevoflurane for the single VCB method. In contrast, the use of

the single VCB method with sevoflurane 7.5% in nitrous oxide 67% is an anaesthesia safe, rapid, reliable and acceptable means of induction of anaesthesia, and a viable alternative to intravenous induction.

References

- 1 Goresky GV, Muir J. Inhalation induction of anaesthesia (Editorial). *Can J Anaesth* 1996; 43: 1085-9.
- 2 Bourne JG. General anaesthesia for out-patients, with special reference to dental extraction. *Proceedings of the Royal Society of Medicine* 1954; 416-22.
- 3 Ruffle JM, Snider MT, Rosenberger JL, Latta WB. Rapid induction of halothane anaesthesia in man. *Br J Anaesth* 1985; 57: 607-11.
- 4 Galloway DW. Rapid inhalation induction (Letter). *Anaesthesia* 1987; 42: 772-3.
- 5 Loper K, Reitan J, Bennett H, Benthuyssen J, Snook L Jr. Comparison of halothane and isoflurane for rapid anaesthetic induction. *Anesth Analg* 1987; 66: 766-8.
- 6 Lamberty JM, Wilson IH. Single breath induction of anaesthesia with isoflurane. *Br J Anaesth* 1987; 59: 1214-8.
- 7 Yurino M, Kimura H. Vital capacity rapid inhalation induction technique: comparison of sevoflurane and halothane. *Can J Anaesth* 1993; 40: 440-3.
- 8 Yurino M, Kimura H. A comparison of vital capacity breath and tidal breathing techniques for induction of anaesthesia with high sevoflurane concentrations in nitrous oxide and oxygen. *Anaesthesia* 1995; 50: 308-11.
- 9 Yurino M, Kimura H. Vital capacity breath technique for rapid anaesthetic induction: comparison of sevoflurane and isoflurane. *Anaesthesia* 1992; 47: 946-9.
- 10 Anonymous. Inhalational induction of anaesthesia - new inspiration? (Editorial) *Lancet* 1986; 2: 84.
- 11 Reves JG, Fragen RJ, Vinik R, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; 62: 310-24.
- 12 Versed® (midazolam HCl) drug insert. Roche Laboratories, Nutley, New Jersey.
- 13 Sloan MH, Conard PF, Karsunky PK, Gross JB. Sevoflurane versus isoflurane: induction and recovery characteristics with single-breath inhaled inductions of anaesthesia. *Anesth Analg* 1996; 82: 528-32.
- 14 Data on file. Abbott Laboratories.
- 15 Stevens WC, Dolan WM, Gibbons RT, *et al.* Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; 42: 197-200.
- 16 Lewis MC, Schauer JC, Gold MI. Single breath induction technique: comparison of sevoflurane and isoflurane (Letter). *Anesth Analg* 1996; 83: 886-91.
- 17 Smith I, Nathanson M, White PF. Sevoflurane - a long-awaited volatile anaesthetic. *Br J Anaesth* 1996; 76: 435-45.