Reports of Investigation

Cost comparison of sevoflurane with isoflurane anesthesia in arthroscopic menisectomy surgery

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Purpose: To determine the "real world" cost of sevoflurane compared with isoflurane in balanced general anesthesia for daycare arthroscopic menisectomy, we prospectively investigated perioperative drug requirement and expense as well as recovery time.

Methods: Following intravenous induction, 40 consenting adult patients randomly received either sevoflurane- or isoflurane-based anesthesia with a standardized gas inflow rate of 3 l·min. Recovery was assessed in the postanesthetic recovery room (PARR) in a double-blind manner at 15 min intervals using the Aldrete scoring system until patients met discharge criteria.

Results: Patient demographics, anesthetic duration, volatile potency and adjunct drug requirements were similar in the two groups. Total perioperative drug cost per patient was CAN\$38.10 ± 10.13 (mean ± SD) for the sevoflurane group and \$23.87 ± 6.59 for the isoflurane group (P <0.01). Although the nonvolatile drug cost was comparable between the two groups, the volatile drug cost per patient was \$19.40 ± 8.80 for sevoflurane and \$4.50 ± 1.90 for isoflurane (P <0.01). This four-fold sevoflurane-to-isoflurane cost difference was the product of two ratios, both based on the volume of liquid anesthetic: the ratio of consumption, 2.1; and the ratio of institutional price, 2.1. Intraoperative hemodynamic response, time until discharge from the PARR and incidences of postoperative nausea and vomiting did not significantly differ between the two groups.

Conclusions: When used to maintain equipotent balanced general anesthesia for daycare arthroscopic menisectomy, volatile consumption and cost were greater for sevoflurane compared with isoflurane. Nonvolatile perioperative drug cost and recovery times were similar, however, in the two groups.

Objectif : Déterminer le coût réel du sévoflurane, comparé à l'isoflurane, pour une anesthésie générale balancée lors d'une méniscectomie arthroscopique en chirurgie d'un jour, par une étude périopératoire prospective des besoins de médicaments et de leur utilisation ainsi que du temps de récupération.

Méthode : Après l'induction intraveineuse de l'anesthésie, 40 adultes volontaires ont reçu au hasard soit du sévoflurane, soit de l'isoflurane selon un débit gazeux standard de 3 L/min. La récupération a été évaluée, à double insu, à la salle de réveil, selon des intervalles de 15 min en utilisant le système de cotation d'Aldrete jusqu'à ce que le patient réponde aux critères de sortie.

Résultats : Les informations personnelles, la durée de l'anesthésie, la puissance des gaz anesthésiques et les besoins supplémentaires de médicaments ont été similaires chez les patients des deux groupes. Le coût périopératoire total des médicaments par patient a été de 38,10 ± 10,13 \$ CAN (moyenne ± écart-type) pour le sévoflurane et de 23,87 ± 6,59 \$ pour l'isoflurane P < 0,01). Le coût de l'agent non volatil était comparable d'un groupe à l'autre, mais l'agent volatil a coûté 19,40 ± 8,80 \$ par patient pour le sévoflurane et 4,50 ± 1,90 \$ pour l'isoflurane (P < 0,01). Cette différence, le sévoflurane coûte quatre fois plus cher que l'isoflurane, est le produit de deux ratios basés sur le volume de l'anesthésique liquide : un premier ratio de consommation, 2:1 et un second ratio de prix du fournisseur, 2:1. La réponse hémodynamique peropératoire, le temps de la récupération en salle de réveil jusqu'au départ et l'incidence de nausées et de vomissements postopératoires n'ont pas montré de différence intergroupe significative.

Conclusion : La consommation d'anesthésique volatil et le coût ont été plus importants pour le sévoflurane que pour l'isoflurane, lors de leur utilisation dans le maintien d'une anesthésie générale balancée équivalente pour une méniscectomie arthroscopique ambulatoire. Le coût périopératoire du médicament non volatil et le temps de récupération ont toutefois été similaires dans les deux groupes.

SINCE 1990, sevoflurane has been marketed as a new inhalational anesthetic with less respiratory irritation and more rapid emergence in comparison to isoflurane.[1,2] While a shortened recovery may decrease postoperative drug cost as well as nursing requirements and quality of life impacts, these potential benefits may be offset by the price of sevoflurane. Drugs with patent protection are more expensive than generic drugs because of ever-increasing research and developmental budgets. Although vaporization calculations *predict* a higher cost for sevoflurane anesthesia,[3–5] the *measured* cost remains largely uncertain. This information is essential to establish the role of sevoflurane in our adult practice.

We have prospectively investigated perioperative drug cost (intraoperative anesthetics and analgesics plus postoperative drugs) by randomizing adult patients for daycare arthroscopic menisectomy to either sevoflurane- or isoflurane-based anesthesia. Anesthetic consequences were also compared – intraoperative hemodynamic response, time to readiness for discharge from the postanesthetic recovery room (PARR) and incidences of postoperative nausea and vomiting – to measure anesthesia depth and estimate clinically significant value related to indirect cost.

Methods

Design

After a pilot study and with approval from the institutional human research committee, we studied 40 patients undergoing general anesthesia for daycare arthroscopic menisectomy in a prospective randomized trial. Patients of either sex, age ≥18 and ≤65 yr, and ASA physical status ≤2 were eligible for study. Following written informed consent, patients were randomly assigned to receive either sevoflurane (*n* = 20) or isoflurane (*n* = 20) as part of a balanced general anesthetic; randomization was computer-generated (Microsoft Excel, version 5.0, Microsoft Corp., Redmont, USA) in blocks of four under the direction of the study monitor. Adjuvant drugs, volatile concentration and the method of airway control were left to the discretion of the anesthesiologist to reflect "real world" cost in our institution. Each patient, however, received the following: a fresh gas flow rate of 3 l·min⁻¹ (N_2O 2 l·min⁻¹, O_2 1 l·min⁻¹) to comply with the recommendation by the manufacturer of sevoflurane in avoiding production of Compound A;[6] and, an intra-articular administration of local anesthetic (20 ml bupivacaine 0.25%) by the surgeon at the end of the procedure. Patients, surgeons, PARR nurses, daycare nurses and data analysts were blinded to group designation.

Data acquisition

Noninhalational perioperative drugs were recorded by the anesthesiologist, the PARR nurse and the daycare nurse in the hospital charts. The study monitor noted the gas (N_2O and O_2) inflow rate and the duration of anesthesia (beginning with the induction of the volatile anesthetic and ending with the removal of the airway assist device in the operating room). An Ohmeda Modulus CD Anesthesia System recorded the following every 20 sec to floppy disk: respiratory rate (RR), heart rate (HR), plus inspired and expired volatile anesthetic concentrations (VI% and VE%, respectively). Noninvasive mean arterial pressures (MAP) were recorded automatically every 3-5 min. Recovery was assessed in the PARR at 15 min intervals using the Aldrete scoring system[7] until patients met discharge criteria (score 9). Postoperative nausea was documented if reported by the patient in response to a standard question: "How are you feeling?"

Determination of inhalational drug costs

Vaporizers were dedicated only to this study to obtain total consumed volumes of liquid sevoflurane and isoflurane. Residual volumes from bottles and vaporisers were measured at the end of the study with a volumetric flask and subtracted from labelled bottle volumes in order to calculate total consumed volume. Then, to assess sampling variability, patient consumed volume was determined with a new method as follows:

$$\begin{array}{c}\text{Patient} \\ \text{volatile consumed} \\ \text{volume}\end{array} = \frac{\Sigma \ (VI\% \ per \ individual \ patient)}{\Sigma \ (VI\% \ per \ entire \ group)} \times \begin{array}{c}\text{Total} \\ \text{volatile consumed} \\ \text{volume}\end{array}$$

Patient volatile cost was calculated from patient consumed volume by using the hospital pharmacy unit cost (in Canadian dollars: $1.20 per ml for sevoflurane and $0.57 per ml for isoflurane; see Table I for all drug prices). However, we did not include expenses related to the following: (i) the purchase of sevoflurane vaporisers; (ii) the conversion of anesthetic gas measuring instruments; and (iii) the maintenance of sevoflurane inventory. N_2O and O_2 costs were calculated as follows:

$$\begin{array}{c}\text{Patient} \\ \text{gas cost}\end{array} = \begin{array}{c}\text{Gas inflow} \\ \text{rate}\end{array} \times \begin{array}{c}\text{Anesthetic} \\ \text{duration}\end{array} \times \begin{array}{c}\text{Unit} \\ \text{cost}\end{array}$$

Determination of non-inhalational drug costs

The cost of all intravenous and oral drugs used in the intra- and postoperative periods were calculated. For single-use vials, the cost was based on the whole vial to include wastage. For multi-use vials, the cost was based on the percentage of the drug volume used.

TABLE I Drug prices in Canadian dollars.

Sevoflurane (250 ml)	300
Isoflurane (100 ml)	57.49
N$_2$O (100 l)	1.25
O$_2$ (100 l)	0.85
Droperidol (5 mg·2 ml⁻¹)	4
Propofol (200 mg·20 ml⁻¹)	8.6
Fentanyl (250 µg·5 ml⁻¹)	1.19
Alfentanil (2.5 mg·5 ml⁻¹)	14.16
Midazolam (5 mg·5 ml⁻¹)	3.43
Rocuronium (50 mg·5 ml⁻¹)	12.75
Succinylcholine (100 mg·5 ml⁻¹)	0.88
Bupivacaine 0.25% (20 ml)	4.11
Morphine (10 mg·10 ml⁻¹)	1.29
Acetaminophen (300 mg) with codeine (30 mg)	0.05

Data are based on the direct cost to our institution from the manufacturer in 1997.

TABLE II Patient demographic data.

	Sevoflurane (n = 20)	Isoflurane (n = 20)
Age (yr)	41 ± 11	38 ± 11
M/F Sex	16/4	17/3
Height (cm)	177 ± 9	179 ± 8
Weight (kg)	82 ± 15	87 ± 13
ASA 1 physical status	20	20

Mean ± SD or number indicating occurrence. No differences between groups.

M: male; F: female; ASA: American Society of Anesthesiologists.

TABLE III GA duration plus intraoperative and PARR drug data.

	Sevoflurane (n = 20)	Isoflurane (n = 20)
GA duration (min)	36 ± 10	40 ± 10
Volatile anesthetic		
VI (%)*	2.0 ± 0.8	1.0 ± 0.3
VE (%)*	1.6 ± 0.6	0.7 ± 0.2
Consumption (ml)*	16.2 ± 7.3	7.8 ± 3.3
N$_2$O 2 l·min⁻¹, O$_2$ 1 l·min⁻¹	20	20
Propofol (mg)	250 ± 120	240 ± 50
Fentanyl (µg)	140 ± 120	100 ± 50
Bupivacaine 0.25%, 20 ml	20	20
Midazolam	9	7
Total mg	12	10.5
Droperidol	2	4
Total mg	2	5
Alfentanil	0	1
Total µg	0	750
Rocuronium	1	0
Total mg	7	0
Succinylcholine	1	1
Total mg	140	60
PARR Fentanyl	2	0
Total µg	100	0
PARR Morphine	1	1
Total mg	4	6
Postop Acetaminophen/codeine	10	12
Total tablets	22	26

Mean ± SD or number, indicating occurrence or total quantity per group. *P < 0.01.

GA: general anesthesia; VI: inspired volatile concentration; VE: expired volatile concentration; PARR: postanesthetic recovery room.

Data analysis and statistical comparisons
A computerized time-series graph of the vital signs for each patient was reviewed by an anesthesiologist, blinded to the group designation, for the following: clinically significant bradycardia (HR <50 bpm) or tachycardia (HR >100 bpm), and hypotension or hypertension (deviation of ± 30% of control-awake MAP). The data, excluding incidences, were described as means (or means of the running average with a time base of five minutes for RR, HR, VI% and VE%) ± SD. Based on the reported minimum alveolar concentration (MAC) of the volatile in N$_2$O 65% in young adults (age ~25 years) for sevoflurane[8] and isoflurane,[9] we compared each VE% by calculating an anesthetic "dose" in 95% of subjects[10] (AD95) as follows:

$$AD95 = 1.25 \times MAC$$

Demographic, drug, monetary and vital sign data were tested where appropriate for normality with the Kolmogorov-Smirnov procedure and compared using the Student's t test. Incidences were compared using a 4-fold contingency table. Statistical significance was concluded with P <0.05.

Results
Patient demographic data (Table II), anesthetic techniques and anesthetic durations (Table III) were similar for the sevoflurane and isoflurane groups. Four surgeons and eight anesthesiologists completed 40 procedures. Following intravenous induction of anesthesia, thirty-nine patients breathed spontaneously through a laryngeal mask airway, whereas in one obese patient the trachea was intubated for aspiration prophylaxis (sevoflurane group).

As expected, based on different potencies, the total volume of liquid anesthetic consumed (sevoflurane 323 ml, isoflurane 156 ml) as well as the average VE% (sevoflurane 1.6 ± 0.6%, isoflurane 0.7 ± 0.2%; P < 0.01; Table III) was greater with sevoflurane. The ratio of VE% to AD95 for each volatile was almost identical (0.91 for sevoflurane and 1.0 for isoflurane),

TABLE IV Perioperative drug cost in Canadian dollars.

	Sevoflurane (n = 20)	Isoflurane (n = 20)
Volatile anesthetic*	19.40 ± 8.80	4.50 ± 1.90
Anesthetic adjuvant drugs	18.34 ± 6.56	19.23 ± 5.48
PARR drugs	0.36 ± 0.58	0.14 ± 0.30
Total drug cost*	38.10 ± 10.13	23.87 ± 6.59

Mean ± SD. *P < 0.01.

TABLE V Intraoperative vital signs and recovery outcomes.

	Sevoflurane (n = 20)	Isoflurane (n = 20)
RR (min^{-1})	16 ± 6	16 ± 3
HR (min^{-1})	63 ± 11	66 ± 12
MAP (mm Hg)	78 ± 19	84 ± 12
MAP ≤70% control	0	0
PARR nausea	3	1
Aldrete ≥9 at 15 min	20	20

Mean ± SD or number indicating occurrence. No differences between groups.
RR = respiratory rate; HR = heart rate; MAP = mean arterial blood pressure.

suggesting equipotency of the sevoflurane and isoflurane concentrations. We further analyzed the ratio of VE% to AD95 during beginning, middle and last thirds of the anesthetics, to assess the adequacy of compensation for the higher solubility of isoflurane.[11] This ratio was comparable between the two groups, suggesting maintenance of equipotent concentrations.

The noninhalational perioperative drug data were similar for the sevoflurane and isoflurane groups (Table III). All patients received propofol for induction and fentanyl for analgesia during the intraoperative period. In PARR, three sevoflurane patients and one isoflurane patient received systemic opioids. Approximately 50% of patients in each group received oral analgesics. No patient required antinauseants.

The sevoflurane patients had the highest cost of volatile anesthetic (sevoflurane $19.40 ± 8.80, isoflurane $4.50 ± 1.90; P < 0.01; see Table IV). A four-fold sevoflurane-to-isoflurane cost difference consisted of the product of two ratios based on the volume of liquid anesthetic: the ratio of consumption, i.e., 2.1 (16.2 ml/7.8 ml; see Table III); and the ratio of institutional price, i.e., 2.1 ($1.20 per ml/$0.57 per ml; see Methods). Nonvolatile perioperative drugs did not differ in expenditure between the two groups. Total perioperative drug cost per patient was then higher with sevoflurane- compared with isoflurane-based anesthesia ($38.10 ± 10.13 and $23.87 ± 6.59, respectively; P < 0.01).

Satisfactory anesthesia and recovery were obtained for all patients (Table V). During anesthesia, the averages for RR, HR and MAP were not different between the sevoflurane and isoflurane groups. In addition, bradycardia, tachycardia, hypotension or hypertension did not occur in either group. Within 15 min after arrival in PARR, all patients met the criteria for discharge to the daycare area. The incidence of postoperative nausea did not differ and no patient vomited.

Discussion

In this randomized general anesthetic trial for daycare arthroscopic menisectomy, we found that volatile consumption and cost in the maintenance of equipotent concentrations was higher with sevoflurane than with isoflurane. In terms of clinical importance, sevoflurane increased the relative volatile consumption by 108% ([16.2 ml - 7.8 ml]/7.8 ml; see Table III) and the relative volatile cost by 331% ([$19.40 - $4.50]/$4.50; see Table IV) compared with isoflurane. The nonvolatile perioperative drug cost, however, was similar in the two groups. In addition, the associated anesthetic consequences of intraoperative hemodynamic response, time to readiness for discharge from PARR and incidences of postoperative nausea and vomiting did not differ between the two groups.

Our monetary results agree with a reported higher cost prediction for sevoflurane based on vaporization calculations. For example, the cost determinations of sevoflurane and isoflurane for 36 min of anesthesia using either a single formula ($14.32 and $3.14, respectively)[3] or a computer simulation ($15.36 and $3.17, respectively)[12] represent 75% of our measured volatile cost (cf. Table IV). Presumably this cost underestimation relates in part to the volatile concentration delivered from the vaporizer, which would be higher than VI% because of gas lost by uptake and breathing circuit overflow.[11] Other reports also predict a higher cost for sevoflurane, but comparing them with our results is difficult because institutional price is not separated from liquid anesthetic volume consumption (cf. references 4, 5). Though contractual confidentiality may restrict publication of drug pricing, proportionate expense (cf. reference 3) is at least needed since drug prices of anesthetics vary widely throughout the world.[13]

Our cost data contradict a recent randomized trial in which measured volatile expense did not vary.[14] In contrast to our findings, the ranges of expired concentrations of sevoflurane and isoflurane (0.9 to 2.2% and 1.1 to 2.5%, respectively, mean not described) were similar, as were the rates of liquid anesthetic volume consumption (0.11 ml·min^{-1} and 0.10 ml·min^{-1}, respectively). This suggests that the concentrations of

sevoflurane and isoflurane were not equipotent, rendering the comparison invalid. In addition, the institutional prices of liquid sevoflurane and isoflurane (US$0.65·ml⁻¹ and $0.57·ml⁻¹, respectively) were approximately the same, again in contrast with our institution. Recently, our sevoflurane-to-isoflurane pricing ratio increased from 2.1 to 5.2. When combined with our measured liquid anesthetic volume consumption ratio, a ten-fold volatile cost difference would now result.

Does the peer-reviewed literature support a similar recovery discharge time following anesthesia with either sevoflurane or isoflurane? At first glance, the answer is uncertain. Most studies follow longer anesthetics with tracheal intubation and may be open-label in the PARR. In addition, anesthesia timing ends and emergence plus extubation timing begins when the inhalational agents are discontinued. However, time from the end of surgery to either removal of the airway device (included in our anesthesia time) or arrival in PARR should ideally be measured. Then, differences in emergence would be clinically important, reflecting patient utility of the operating room instead of known differences in pharmacokinetics. Specifically, two investigations are somewhat suitable for comparison with our results. In a double-blind study with tracheal intubation, shorter extubation and recovery times were reported for sevoflurane following almost two hours of anesthesia.[14] However, the isoflurane patients received relatively more inhalational agent, as discussed in the preceding paragraph, and the extubation timing began when the volatile was stopped. In contrast, an open-label study with data entry, data analysis and financial support by the manufacturer of sevoflurane, as well as tracheal intubation and anesthesia times closer to our results, reported a shorter emergence time without a difference in extubation time or recovery time.[15] In this latter study, the isoflurane patients had longer anesthesia times, a result that was not reported in the abstract, and both the emergence and extubation timing began when the agents were discontinued.

What are the potential limitations in our investigation? We did not assess the value of sevoflurane's nonpungency in inhalational inductions.[16] In addition, we may have missed a difference in the duration of operating room emergence, as outlined above. Furthermore, we did not use low gas inflow rates even though rebreathing reduces volatile consumption. This latter decision related to two concerns. Isoflurane takes longer than sevoflurane to reach a constant anesthetic alveolar concentration, especially at low gas inflow rates.[11] Experimentally, we had to standardize either

uptake characteristics (unrealistic) or fresh gas flow rates.[17] As a compromise, we could have used a higher fresh gas flow rate for the initial wash-in and a lower gas inflow rate for maintenance. However, transient renal injury from four hours of 1.25 MAC sevoflurane has been reported in human adults with a gas inflow rate of 2 l·min⁻¹.[18] Besides contradicting the manufacturer's recommendation (see Methods), nephrotoxicity with a lower gas inflow rate has not been fully investigated.

In conclusion, the consumption and cost of sevoflurane were greater than for isoflurane when used to maintain equipotent volatile concentrations during balanced general anesthesia for daycare arthroscopic menisectomy. However, we were unable to demonstrate a clinically important benefit for sevoflurane in this investigation. Our data emphasize the necessity to complete prospective randomized cost and benefit comparisons of equipotent concentrations of standard inhalational anesthetics with new agents before their full introduction.

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