J Anesth (2013) 27:468–471
DOI 10.1007/s00540-012-1536-x

SHORT COMMUNICATION

A prospective randomized multicenter comparative study of BLM-240 (desflurane) versus sevoflurane in Japanese patients

Junzo Takeda · Akiyoshi Namiki · Makoto Ozaki · Kazuhiko Fukuda · Kiyoshi Morita · Yuichi Kanmura · Michiaki Yamakage · Takami Komatsu · Eiichi Inada · Ryoichi Kawate · Masahiro Kanazawa · Atsuhiro Sakamoto · Shoichi Uezono · Shigehito Sato · Kimitoshi Nishiwaki · Yoshikazu Miyamoto · Hideki Nakatsuka · Nobuhiko Yasuda · Baxter BLM-240 Study Team

Received: 24 July 2012 / Accepted: 22 November 2012 / Published online: 10 December 2012

Abstract The present study was conducted to evaluate the efficacy and safety of BLM-240 (desflurane) in comparison to sevoflurane in Japanese patients. A total of 216 patients were enrolled in this randomized comparative study at 15 medical institutions. The patients received either BLM-240 with 50–70 % N_2O in O_2 ($n = 111$), BLM-240 with 30 % O_2 in air ($n = 55$), or sevoflurane with 50–70 % N_2O in O_2 ($n = 50$). Efficacy was evaluated by an efficacy rate based on an efficacy evaluation criteria and recovery time to extubation from the discontinuation of the anesthetics. Safety was evaluated by incidence of adverse drug reactions (ADR) and other clinical indicators. The efficacy rate of BLM-240 was 98.8 % (164/166 patients), indicating that BLM-240 is effective as an anesthetic. Time from discontinuation of anesthetic delivery to extubation was 9.7 ± 0.6 min in the BLM-240/N_2O group and 14.3 ± 0.9 min in the sevoflurane/N_2O group, meeting the pre-defined non-inferiority criteria of BLM-240 to sevoflurane. There was no statistically significant difference in the incidence of total ADR between

J. Takeda (✉)
Department of Anesthesiology, School of Medicine, Keio University, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: jtakeda@z3.keio.jp

A. Namiki · M. Yamakage
Department of Anesthesiology, Sapporo Medical University School of Medicine, Hokkaido, Japan

M. Ozaki
Department of Anesthesiology, Tokyo Women's Medical University, Tokyo, Japan

K. Fukuda
Department of Anesthesiology, Kyoto University Hospital, Kyoto, Japan

K. Morita · H. Nakatsuka
Department of Anesthesiology and Resuscitology, Okayama University Hospital, Okayama, Japan

Y. Kanmura
Department of Anesthesiology and Critical Care Medicine, Kagoshima University Faculty of Medicine, Kagoshima, Japan

T. Komatsu
Department of Anesthesiology, University of Tokyo, Tokyo, Japan

E. Inada
Department of Anesthesiology, Juntendo University School of Medicine, Tokyo, Japan

R. Kawate
Department of Anesthesia, NTT Medical Center Tokyo, Tokyo, Japan

M. Kanazawa
Department of Anesthesiology, Tokai University, Kanagawa, Japan

A. Sakamoto
Department of Anesthesiology, Nippon Medical School, Tokyo, Japan

S. Uezono
Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

S. Sato
Department of Anesthesiology and Resuscitology, Hamamatsu University School of Medicine, Shizuoka, Japan

K. Nishiwaki
Department of Anesthesiology, Nagoya University Hospital, Aichi, Japan

the BLM-240 group (62.0 %) and sevoflurane group (48.0 %). The results indicate that BLM-240 is an effective and safe inhalation anesthetic in Japanese patients.

Keywords Desflurane · Sevoflurane · Inhalation · Anesthetic

BLM-240 (desflurane) has been widely used in clinical practice outside of Japan as a volatile inhaled anesthetic in a variety of surgeries including ambulatory, cardiovascular, geriatric and pediatric surgeries [1–4]. In addition, the low solubility of BLM-240 suggests that the recovery from anaesthesia is more rapid with BLM-240 than any other volatile anesthetic in clinical use including sevoflurane [5–7].

In Japan, the previous safety and pharmacokinetic studies suggested that the pharmacokinetic and safety profiles of BLM-240 in Japanese subjects were similar to those obtained in foreign studies [5, 8]. In order for BLM-240 to be officially used in Japan, a further clinical study is warranted to confirm the safety and efficacy of BLM-240 in Japanese patients. Therefore, a prospective, randomized, multicenter comparative study was designed to evaluate the efficacy and safety of BLM-240 in comparison with sevoflurane in Japanese patients undergoing a variety of surgical procedures.

The study was approved by the Institutional Review Board of each medical institution, and written informed consents were obtained from all of the patients before their enrollment into this study. Patients undergoing elective surgeries with American Society of Anesthesiologists (ASA) Physical Status I–III and aged 20–69 years were included. Key exclusion criteria included patients requiring regional or local anesthesia, those with a serious hepatic, renal, or cardiovascular disorder, and those with a history of malignant hyperthermia. Patients were randomized to receive either BLM-240 with 50–70 % N_2O in O_2 ($n = 111$), BLM-240 with 30 % O_2 in air ($n = 55$), or sevoflurane with 50–70 % N_2O in O_2 ($n = 50$). Anesthesia was induced with propofol (2.0–2.5 mg/kg) and fentanyl (1.5–8.0 μg/kg). In addition, vecuronium (0.08–0.10 mg/kg) was used to facilitate tracheal intubation. Inhalation of BLM-240 was initiated at 3 % while sevoflurane was initiated at 1 %. BLM-240 or sevoflurane concentrations were adjusted to maintain anesthesia at clinically adequate levels at the anesthesiologist's discretion. Additional doses of fentanyl and vecuronium were allowed. Vital signs, electrocardiograms, bispectral index (BIS), oxygen saturation of peripheral artery (SpO_2), minute ventilation, end-tidal CO_2 concentration and anesthetic concentrations were monitored at 5-min intervals during anesthesia. Rescue medications such as ephedrine and nicardipine were allowed only when blood pressure and heart rate could not be maintained without their usage. For at least 10 min before discontinuation of the inhalational anesthetic, the end-tidal concentrations of BLM-240 and sevoflurane were maintained at 3–6 and 1–2 %, respectively. Positive response to name calling and possibility of extubation were assessed at 1-min intervals after the discontinuation of anesthetic administration. Ability to state birth date was assessed at 1-min intervals after extubation. In addition, recovery time to attaining a Modified Aldrete score ≥ 8 was also monitored every 5 min. An efficacy grade of either "excellent effectiveness", "sufficient effectiveness", "moderate effectiveness", "insufficient response", "inadequate response" or "unevaluable" was given to each case according to a pre-determined efficacy rating scale based on the assessments of body movement, recall/memory, rescue treatment and blood pressure/heart rate. Cases given "moderate effectiveness" or higher effectiveness were considered as "effective". An efficacy rate was calculated as the ratio of the "effective" cases in the Full Data Set (all patients who received either BLM-240 or sevoflurane). If the lower limit of the 95 % confidence interval (CI) of the efficacy rate was higher than 90 %, the anesthetic was determined as having effective anesthetic actions. In addition, recovery time to extubation after discontinuation of anesthetics was used to verify non-inferiority of BLM-240 to sevoflurane. If the upper limit of the 95 % CI of difference between BLM-240/N_2O and sevoflurane/N_2O groups in recovery time to extubation was less than 1.0 min, it was determined that BLM-240 was not inferior to sevoflurane. Safety was evaluated by incidence of adverse events including clinical signs and symptoms, vital signs, and clinical laboratory abnormalities. In case of an adverse event, seriousness, severity and relationship to anesthetics were also recorded. All statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute, Japan).

A total of 216 patients were enrolled in this study. There was no significant demographic difference between the overall BLM-240 group (BLM-240/N_2O and BLM-240/O_2 groups combined) and the sevoflurane/N_2O group, or between the BLM-240/N_2O group and the sevoflurane/N_2O group (Table 1). The efficacy rate in the overall BLM-240 group combining BLM-240/N_2O and BLM-240/O_2 is 98.8 % (95 % CI: 95.7–99.9 %), meeting the pre-defined

Y. Miyamoto
Department of Anesthesiology, Osaka University Hospital, Osaka, Japan

N. Yasuda
President's Office, Jikei University, Tokyo, Japan

Baxter BLM-240 Study Team
Baxter Limited, Tokyo, Japan

Table 1 Patient Demographics

	BLM-240 group ($n = 166$)		Sevoflurane/N_2O group ($n = 50$)
	BLM-240/N_2O ($n = 111$)	BLM-240/O_2 ($n = 55$)	
Sex (n, %)			
Male	51 (45.9)	20 (36.4)	19 (38.0)
Female	60 (54.1)	35 (63.6)	31 (62.0)
ASA physical status [I/II/III, n (%)]	77 (69.4)/ 34 (30.6)/0	36 (65.5)/ 19 (34.5)/0	37 (74.0)/ 13 (26.0)/0
Age (years)	49 ± 12.2	47 ± 13.6	46 ± 13.4
BMI (kg/m^2)	22 ± 2.7	22 ± 3.0	23 ± 3.5
Operative site (n, %)			
Chest	11 (9.9)	6 (10.9)	6 (12.0)
Abdomen	37 (33.3)	19 (34.5)	17 (34.0)
Joints	19 (17.1)	9 (16.4)	10 (20.0)
Back	11 (9.9)	2 (3.6)	4 (8.0)
Neck	33 (29.7)	19 (34.5)	13 (26.0)
Duration of surgery (n, %)			
<2 h	63 (56.8)	28 (50.9)	30 (60.0)
2–<4 h	39 (35.1)	22 (40.0)	19 (38.0)
≥4 h	9 (8.1)	5 (9.1)	1 (2.0)
Fentanyl dose (mg/kg/h)	1.14 ± 0.40	1.29 ± 0.45	1.13 ± 0.50

Values are expressed as mean ± SD, number or percentages (%). No significant differences between the BLM-240 group and sevoflurane/N_2O group, or BLM-240/N_2O and sevoflurane/N_2O group based on Fisher's exact test, Wilcoxon two-sample test or two-sample t-test

success criteria for confirming the efficacy of BLM-240. Recovery time to extubation adjusted by operative site and surgery time were 9.7 ± 0.6 min in the BLM-240/N_2O group and 14.3 ± 0.9 min in the sevoflurane/N_2O group, and difference between the 2 groups was −4.6 min (95 % CI: −6.6 to −2.7). The upper limit of the 95 % CI of difference in recovery time to extubation between the 2 groups was lower than the predetermined non-inferiority margin (delta: 1.0 min), demonstrating that BLM-240 was not inferior to sevoflurane. Time to awakening, stating the birth date and reaching Modified Aldrete score ≥8 from discontinuation of anesthetics were all shorter in the BLM-240 groups than those in the sevoflurane group (Table 2). In addition, no difference was found between the BLM-240 group and the sevoflurane group in the time profile of BIS or the frequency of rescue treatment. BIS were mostly maintained between 40 and 50 during anesthesia. A total of 195 adverse drug reactions (ADR), of which the relationship to anesthetics could not be denied, occurred in 103 of 166 subjects (62.0 %) in the overall BLM-240 group and 44 ADRs occurred in 24 of 50 subjects (48.0 %) in the sevoflurane/N_2O group. There was no significant difference in the incidence of total ADR between the 2 groups using a chi-square analysis. The most frequently observed ADRs include nausea, vomiting, increased blood bilirubin, decreased blood pressure and decreased heart rate. Among them, the incidence of increased blood bilirubin in the overall BLM-240 group (11.4 %; 19/166 subjects) was significantly higher than that in the sevoflurane group (0.0 %; 0/50) ($P = 0.0085$). Those increased blood

Table 2 Awakening/recovery from discontinuation of anesthetics

Treatment group	Mean ± SD (min)	P value*	
		BLM-240 combined	BLM-240 N_2O only
Time to awakening			
BLM-240 group ($n = 166$)	6.8 ± 4.0	NA	NA
BLM-240/N_2O ($n = 111$)	7.2 ± 3.7	NA	NA
BLM-240/O_2 ($n = 55$)	6.2 ± 4.6	NA	$P = 0.1500$
Sevoflurane group ($n = 50$)	10.4 ± 5.5	$P < 0.0001$	$P = 0.0000$
Time to stating the birth date			
BLM-240 group ($n = 166$)	11.4 ± 5.4	NA	NA
BLM-240/N_2O ($n = 111$)	11.8 ± 5.3	NA	NA
BLM-240/O_2 ($n = 55$)	10.6 ± 5.6	NA	$P = 0.1768$
Sevoflurane group ($n = 50$)	16.2 ± 8.7	$P < 0.0001$	$P = 0.0001$
Time to reaching a modified Aldrete score ≥8			
BLM-240 group ($n = 166$)	13.6 ± 5.2	NA	NA
BLM-240/N_2O ($n = 111$)	13.9 ± 4.8	NA	NA
BLM-240/O_2 ($n = 55$)	13.1 ± 6.0	NA	$P = 0.387$
Sevoflurane group ($n = 50$)	18.7 ± 8.4	$P < 0.0001$	$P < 0.0001$

* P values calculated from 2-sample t-test comparing either BLM-240/O_2 versus BLM-240/N_2O, Sevoflurane versus BLM-240 combined group, or sevoflurane BLM-240/N_2O group

NA not applicable

bilirubin all recovered to baseline or normal ranges within 7 days after surgery without any treatment. Also, no clinical symptoms related to hepatic dysfunction such as jaundice and hepatitis were observed.

The results of the present study confirm that BLM-240 delivered with or without N_2O is an effective anesthetic with more rapid recovery compared to sevoflurane in Japanese patients undergoing general surgery. BLM-240 will provide a wider option to Japanese anesthesiologists given its more rapid recovery from and flexibility in maintenance of anesthesia. Given that BLM-240 is widely used for day surgery outside of Japan, it may promote day surgery in Japan. The present study also confirms that the overall safety profile of BLM-240 delivered with or without N_2O is similar to that of sevoflurane delivered with N_2O in Japanese patients. In this study, a transient increase in blood bilirubin was observed in the BLM-240 group (19/166 subjects). However, no clinically significant symptoms were observed. The reason for this transient increase could not be determined, but such events were observed with the use of other anesthetics [9]. In Japan, sevoflurane and other volatile anesthetics had been approved when N_2O was used concomitantly. In the present study, the safety and efficacy of BLA-240 was demonstrated not only with N_2O but also without N_2O. This will also provide an official wider option for Japanese anesthesiologists.

In conclusion, BLM-240 can be used effectively and safely in Japanese patients. In addition, the shorter recovery properties of BLM-240 compared to sevoflurane were demonstrated in Japanese patients.

Conflict of interest Junzo Takeda and Nobuhiko Yasuda have received a consulting fee from Baxter Ltd and all the other authors have no conflict of interest. This study was sponsored by Baxter Healthcare Corporation.

References

1. Saros GB, Doolke A, Anderson RE, Jakobson JG. Desflurane vs. sevoflurane as the main inhaled anaesthetic for spontaneous breathing via a laryngeal mask for varicose vein day surgery: a prospective randomized study. Acta Anaesthesiol Scand. 2006;50:549–52.
2. Meco M, Cirri S, Gallazzi C, Magnani G, Cosseta D. Desflurane preconditioning in coronary artery bypass graft surgery a double-blinded, randomised and placebo-controlled study. Eur J Cardiothorac Surg. 2007;32:319–25.
3. Rörtgen D, Kloos J, Fries M, Grottke O, Rex S, Rossaint R, Coburn M. Comparison of early cognitive function and recovery after desflurane or sevoflurane anaesthesia in the elderly. Br J Anaesth. 2010;104:167–74.
4. Makkar KJ, Ghai B, Bhardwaj N, Wig J. Minimum alveolar concentration of desflurane with fentanyl for laryngeal mask airway removal in anesthetized children. Pediatric Anesth. 2012;22:335–40.
5. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg. 1989;69:370–3.
6. Bilotta F, Doronzio A, Cuzzone V, Caramia R, Rosa G, PINOCCHIO Study Group. Early postoperative cognitive recovery and gas exchange patterns after balanced anesthesia with sevoflurane or desflurane in overweight and obese patients undergoing craniotomy: a prospective randomized trial. J Neurosurg Anesthesiol. 2009;21:207–13.
7. McKay RE, Malhotra A, Cakmakkaya OS, Hall KT, McKay WR, Apfel CC. Effect of increased body mass index and anaesthetic duration on recovery of protective airway reflexes after sevoflurane vs desflurane. Br J Anaesth. 2010;104:175–82.
8. Baxter company internal report. A final report of the safety and pharmacokinetics of BLM-240 in surgery patients. 2009.
9. Nishiyama T, Yokoyama T, Hanaoka K. Effects of sevoflurane and isoflurane anesthesia on arterial ketone body ratio and liver function. Acta Anaesthesiol Scand. 1999;43:347–51.