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World Journal of Anesthesiology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wja@wjgnet.com
http://www.wjgnet.com

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BRIEF ARTICLE

Comparison between intrathecal hyperbaric bupivacaine and levobupivacaine for ambulatory knee arthroscopy

Ozlem Sagir, Sabri Ozaslan, Mehmet Erduran, Yucel Meric, Ismail Aslan, Ahmet Koroglu

Ozlem Sagir, Yucel Meric, Ismail Aslan, Ahmet Koroglu, Department of Anesthesiology and Reanimation, Faculty of Medicine, Balikesir University, 10145 Balikesir, Turkey
Sabri Ozaslan, Department of Anesthesiology and Reanimation, Erpa Hospital, 20010 Denizli, Turkey
Mehmet Erduran, Department of Orthopedics and Traumatology, 9 Eylul University, Faculty of Medicine, 35340 Izmir, Turkey
Author contributions: Sagir O designed and conducted the study; Sagir O, Ozaslan S, Meric Y and Aslan I wrote the manuscript; Ozaslan S and Erduran M helped design the study; Ozaslan S and Koroglu A analyzed the data; Erduran M performed the surgery; Meric Y and Aslan I collected the data; Koroglu A approved the final manuscript.
Correspondence to: Ozlem Sagir, MD, Assistant Professor, Department of Anesthesiology and Reanimation, Faculty of Medicine, Balikesir University, Cagis Campus, 10145 Balikesir, Turkey. ozlemsagir@yahoo.com
Telephone: +90-532-7609927 Fax: +90-266-61214
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Abstract

AIM: To compare the effect of hyperbaric levobupivacaine and bupivacaine on the quality of the block, patient satisfaction, and discharge time in patients undergoing arthroscopic knee surgery under unilateral spinal anesthesia.

METHODS: One hundred and thirty-two patients, American Society of Anaesthesiologists Ⅰ or Ⅱ, scheduled for elective ambulatory knee arthroscopy were randomly assigned to four double-blind groups. To achieve a unilateral spinal block, Group BF received 5 mg of hyperbaric bupivacaine plus 20 μg of fentanyl intrathecally, Group LF received 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl intrathecally, Group B received 5 mg of hyperbaric bupivacaine intrathecally, and Group L received 5 mg of hyperbaric levobupivacaine intrathecally. The level and duration of the sensory block, the intensity and duration of the motor block, the time to first analgesic requirement, and the time elapsed until the patient's discharge were recorded. Hemodynamic values and adverse effects were also recorded.

RESULTS: The duration of time needed to reach the T12 dermatome level was significantly longer in Group L [7 (3-20) min] than in Group B [6 (3-12) min] (P = 0.006). The maximum sensory level reached on the side undergoing the operation was significantly higher in Group BF than in Group B (P < 0.05). The intensity of the motor blockade was greater in Group BF than in Group LF and L. Complete recovery from motor blockade occurred earlier in Groups LF [75 (45-165) min] and L [63 (35-120) min] than in Group BF [115 (60-180) min] (P < 0.05). The length of time needed for the sensory block to regress to the level of S2 was shorter in Group L (154 ± 50) than in Group BF (192 ± 66) (P < 0.05). The quality of the block was significantly lower in Group L than in Groups BF, LF and B (P = 0.012, P = 0.003, and P < 0.001, respectively). The time elapsed until Visual Analog Scale ⩾ 4 was significantly shorter in Group L (110 ± 48) than in Groups BF (200 ± 60), LF (156 ± 61) and B (162 ± 52) (P < 0.05). The time elapsed until the patient's discharge was shorter in Groups B (244 ± 54) and L (229 ± 55) than in Group BF (288 ± 64) (P = 0.021 and P = 0.001, respectively). There were no differences among the groups regarding hemodynamic parameters and adverse events, except for pruritus. The occurrence of pruritus was significantly more frequent in Groups BF and LF than in other groups.

CONCLUSION: In conclusion, 5 mg of hyperbaric bupivacaine and 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl provided a better spinal anesthesia than 5 mg of hyperbaric levobupivacaine alone.

Key words: Spinal anesthesia; Knee arthroscopy; Outpatient surgery; Bupivacaine; Levobupivacaine

Core tip: Arthroscopic knee surgery is a common procedure performed in the ambulatory setting. The primary goals of the anesthetic techniques used in ambulatory surgery are to reduce anesthetic complications and to allow for early patient discharge. The aim of this study was to compare the effect of low dose hyperbaric bupivacaine and levobupivacaine, with and without fentanyl, on the quality of the block, patient satisfaction, and the time elapsed until discharge in patients undergoing arthroscopic knee surgery under unilateral spinal anesthesia.

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INTRODUCTION

Arthroscopic knee surgery is one of the most frequently performed ambulatory orthopedic surgeries. The main goals of the anesthetic techniques used in ambulatory surgery are to reduce anesthetic complications, provide adequate postoperative analgesia and allow for early patient discharge[1].

Spinal anesthesia is often preferred for lower extremity surgery because of the procedure's low level of difficulty, better postoperative analgesia and reduced incidences of nausea or vomiting[2]. Long-acting local anesthetics such as bupivacaine and levobupivacaine have been widely used in ambulatory surgery thanks to the development of the low-dose spinal anesthesia technique[3,4]. However, when small doses of local anesthetics are used, an adjuvant must be given to improve the quality of the block and decrease the risk of a failed block. Different adjuvants such as lipid soluble opioids can be added to the local anesthetics[5].

Levobupivacaine, the S-enantiomer of racemic bupivacaine, is approximately equipotent with bupivacaine when used in a similar concentration and dose. At the same time, levobupivacaine is a weaker cardiac and central depressant[6,7]. Studies comparing the different doses and forms of levobupivacaine and bupivacaine for ambulatory arthroscopic surgery have been published[8,9]. However, there is no study comparing these two drugs in the context of arthroscopic knee surgery.

We hypothesized that levobupivacaine administered *via* spinal anesthesia for arthroscopic knee surgery would provide less motor blockade and earlier patient discharge compared to bupivacaine.

The primary outcome of this study was to compare the effect of low dose hyperbaric levobupivacaine and bupivacaine, with and without fentanyl, on the time elapsed until discharge in patients undergoing arthroscopic knee surgery under unilateral spinal anesthesia. The effect of these anesthetics on the quality of the block and patient satisfaction were also compared as a secondary outcome.

MATERIALS AND METHODS

With the approval of the Institutional Ethical Committee, written, informed consent was obtained from all patients. One hundred and thirty-two patients with American Society of Anaesthesiologists (ASA) physical status Ⅰ or Ⅱ, aged 18-65 years, measuring 150-185 cm in height, and scheduled for elective ambulatory knee arthroscopy were included in this prospective, double-blind, randomized controlled study. The number of patients enrolled in this study was determined by considering the relevant literature[6,10]. Patients were excluded when they met one or more of the following criteria: history of a severe renal, hepatic, or cardiac disease; a neurologic or psychiatric condition; a coagulation defect; sepsis or a local infection at the site of the lumbar puncture; and/or any hypersensitivity to local anesthetics or opioids.

Patients were randomized to one of four groups to receive spinal hyperbaric bupivacaine or hyperbaric levobupivacaine, with or without fentanyl (Figure 1). Randomization was performed using a random number table. The local anesthetic solution was prepared aseptically by an anesthetist who was blinded to the study shortly before the spinal injection. Group BF received 5 mg (1 mL) of hyperbaric bupivacaine (Marcaine Heavy 0.5% AstraZeneca) with 20 μg of fentanyl (0.4 mL), Group LF received 5 mg (1 mL) of hyperbaric levobupivacaine with 20 μg of fentanyl (0.4 mL), Group B received 5 mg (1 mL) of hyperbaric bupivacaine with 0.4 mL of sterile water, and Group L received 5 mg (1 mL) of hyperbaric levobupivacaine with 0.4 mL of sterile water. The hyperbaric levobupivacaine solution was prepared by an anesthesiologist who was not involved in further patient care. This solution was composed of 2 mL of plain 0.75% levobupivacaine (Chirocaine: levobupivacaine hydrochloride, Abbott, United Kingdom), 0.8 mL of 30% dextrose, and 0.2 mL of normal saline solution, achieving a final concentration of 0.5% levobupivacaine with glucose. The total syringe volume was 1.4 mL in all four groups.

Patients received no premedication. Pulse oximetry (SPO_2) values, non-invasive blood pressure (NIBP) measurements, and electrocardiogram (ECG) tracings were monitored in all patients. Heart rate, SPO_2 and NIBP were recorded before spinal anesthesia, every 3 min during the first 15 min of the spinal anesthesia, and then every 5 min during the remainder of the surgery. After inserting a 20 gauge *iv* cannula in the dorsum of the hand, 0.5 mL/kg of 0.9% normal saline was preloaded intravenously in all patients. The patients were placed in the lateral decubitus position, and their operated sides were positioned inferiorly. Spinal anesthesia was performed at the L4-5 intervertebral area using the mid-line approach with a 25 gauge Whitacre spinal needle. Correct needle

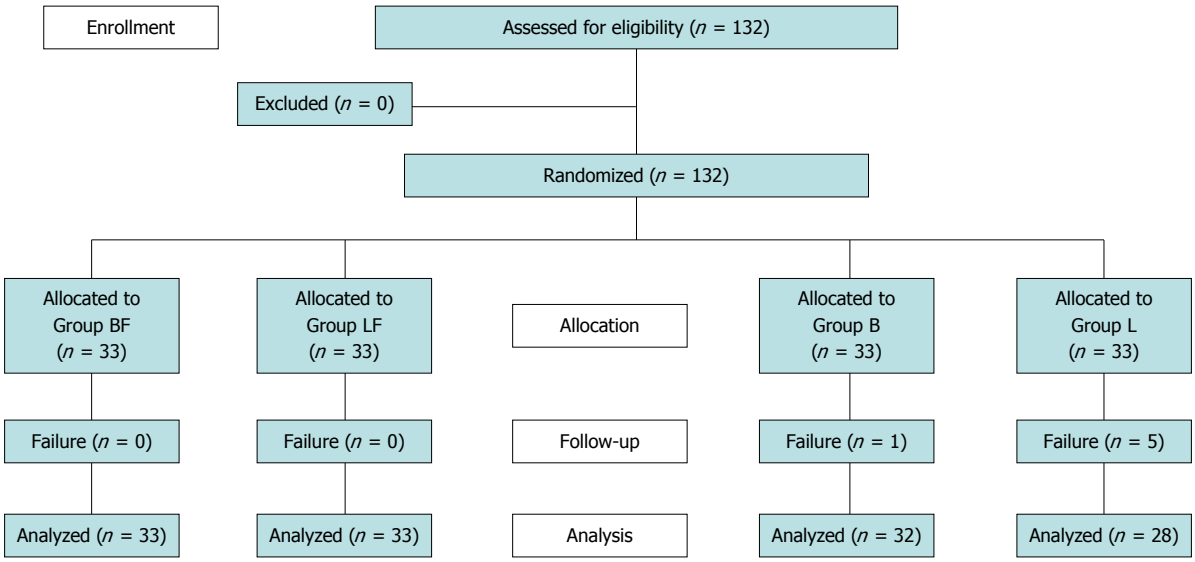

Figure 1 Flowchart. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine.

positioning was confirmed with the free flow of cerebrospinal fluid, and the anesthetic solutions were injected slowly without barbotage. The lateral decubitus position was maintained for 10 min from the start of the injection to provide selective spinal anesthesia. Afterwards, patients were turned to supine position, and surgery was started as soon as the analgesic level reached T12. In the case of insufficient anesthesia during the procedure, fentanyl (1 μg/kg), midazolam (0.05 mg/kg) or both in *iv* formulations were used. If the pain was not controlled with an *iv* bolus of fentanyl and/or midazolam, general anesthesia was administered. Three liters of oxygen per minute was given *via* nasal cannula until the end of the surgical procedure. The anesthesiologist who performed the spinal anesthesia and evaluated the quality of the block was blinded to the study solution received by each group.

The quality of anesthesia was assessed by testing for sensory and motor blockade. Sensory blockade was evaluated by pinprick on each side of the mid-clavicular line, and motor blockade was evaluated *via* the 4-point modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex the knees and 3 = inability to flex the ankle joints). These tests were performed bilaterally every 3 min up to 15 min and then at 5 min intervals until the end of the operation. Postoperatively, these tests were done every 15 min until the sensory block regressed to the level of S2. The following lengths of time were recorded: achievement of a sensory block at the level of T12, maximum spread of the sensory block, highest dermatome level reached, regression to the level of S2, motor blockade levels, regression of the motor blockade, first analgesic requirement and discharge time. Postoperatively, patients who had a Visual Analog Scale (VAS) score ⩾ 4 were given 50 mg of *iv* dexketoprofen trometamol, and the time was recorded as the first analgesic requirement time. Home discharge criteria included stable vital signs, the absence of nausea or vomiting, minimal or no pain, the ability to tolerate liquids by mouth, and the ability to walk and void spontaneously. Complications such as hypotension, bradycardia, nausea, vomiting, shivering and pruritus were also noted.

Hypotension was defined as a decrease in systolic blood pressure > 30% from baseline and was initially treated with a rapid infusion of 250 mL of normal saline. In patients who did not respond to this treatment, 5 mg of *iv* ephedrine was given. Bradycardia was defined as a heart rate < 45 beat/min and was treated with 0.5 mg of *iv* atropine. Nausea and vomiting were treated with 10 mg of *iv* metoclopramide. Pruritus was assessed by a 4-point scale, where 0 = no pruritus, 1 = mild, 2 = moderate, 3 = severe pruritus. Moderate and severe pruritus was treated with *iv* naloxone. Shivering was treated by warming the skin surface. All patients underwent operations by the same experienced surgeon. The satisfaction of the patient and the surgeon regarding the anesthetic technique used was assessed with a 2-point scale, where 1 = satisfied (*i.e.*, "I will accept to undergo the same procedure if it is required in the future") and 2 = unsatisfied (*i.e.*, "I would prefer the use of a different anesthetic technique in future operations").

The quality of the spinal block was evaluated according to the need for additional *iv* analgesics and sedatives: adequate spinal block = neither sedatives nor analgesics were required to complete the surgery; inadequate spinal block = additional analgesia or sedation was required to complete the surgery (0.001 mg/kg bolus of *iv* fentanyl or 0.05 mg/kg bolus of *iv* midazolam); failed spinal block = general anesthesia was required to complete the surgery.

The day after surgery, the patients were contacted *via* telephone by a blinded research assistant and asked whether they had experienced headache, backache, or dysesthesia in the lower limbs or buttocks.

Table 1 Patient characteristics, duration of surgery and failed spinal blocks (*n* = 33)

Variables	Group BF	Group LF	Group B	Group L	*P* value
Gender (M/F)	16/17	13/20	12/21	14/19	0.779
Age (yr)	45 (11)	46 (12)	44 (12)	47 (11)	0.863
Height (cm)	165 (8)	168 (9)	165 (8)	165 (9)	0.664
Weight (kg)	79 (12)	77 (11)	76 (12)	80 (11)	0.253
ASA (Ⅰ/Ⅱ)	25/8	22/11	25/8	26/7	0.699
Duration of surgery (min)	50 (40-60)	60 (35-60)	50 (30-60)	55 (40-60)	0.621
Failed spinal block	0	0	1	5[a]	0.008[a]

Data are presented as the median (min-max), SD, or frequencies. [a]$P < 0.05$ compared with Group hyperbaric bupivacaine plus fentanyl (BF), Group hyperbaric levobupivacaine plus fentanyl (LF) and Group hyperbaric bupivacaine (B). L: Hyperbaric levobupivacaine; M: Male; F: Female; ASA: American Society of Anaesthesiologists.

Table 2 Quality of sensory and motor blocks and post-anesthesia care unit variables per group

Variables	Group BF (*n* = 33)	Group LF (*n* = 33)	Group B (*n* = 32)	Group L (*n* = 28)
Sensory block				
Onset to T12 (min)	6 (3-15)	6 (3-15)	6 (3-12)	7 (3-20)[e]
Highest level of sensory block (dermatome)	T8 (T12-T4)	T10 (T12-T4)	T10 (T12-T4)[a]	T10 (T12-T4)
Time to maximum sensory block (min)	15 (6-35)	12 (6-50)	13 (6-35)	20 (6-40)[c]
Sensory regression	192 ± 66	173 ± 53	179 ± 47	154 ± 50[a]
Motor block				
Time to maximum motor block (min)	9 (3-20)	12 (3-25)	9 (3-25)	12 (3-35)
Motor block regression (min)	115 (60-180)	75 (45-165)[a]	95 (40-150)	63 (35-120)[a,e]
Time to micturition (min)	196 ± 57	174 ± 54	164 ± 45	151 ± 52[a]
Time to VAS ⩾ 4	200 ± 60	156 ± 61[a]	162 ± 52[a]	110 ± 48[a,c,e]
Time to discharge	288 ± 64	260 ± 61	244 ± 54[a]	229 ± 55[a]

Data are presented as the median (min-max) or mean ± SD. [a]$P < 0.05$ compared with Group BF; [c]$P < 0.05$ compared with Group LF; [e]$P < 0.05$ compared with Group B. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine; VAS: Visual Analog Scale.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS 15.0; SPSS, Inc., Chicago, IL, United States). The Kolmogorov Smirnov test was used to assess whether the data were normally distributed. Numerical results were expressed either as a mean ± SD or as a median and range, when appropriate. Nominal data were presented as frequencies. Categorical data in each study group were compared using a χ^2 test or Fisher's exact test. The numerical data were compared between study groups with the Kruskall-Wallis test, followed by the Mann-Whitney *U* test, the Bonferroni correction test, and a One-way ANOVA with the Tukey HSD test. In the case of hemodynamic changes within the study groups, repeated measures analysis of variance was performed. In general, a *P* value of < 0.05 was considered statistically significant. However, the significance level of $P < 0.008$ was determined using a Bonferroni correction for multiple comparison test.

Post-analysis power calculation reached 93%, $\alpha = 0.05$ (1-tailed), with the 33 patients included in Group BF and LF (mean times elapsed until discharge were "288 ± 64" and "260 ± 61", respectively), 32 patients included in Group B (mean time elapsed until discharge was "244 ± 54") and 28 patients included in Group L (mean time elapsed until discharge was "229 ± 55").

RESULTS

There was no statistically significant difference between the four study groups regarding demographic parameters, age, weight, height, sex, and ASA classification (Table 1). Spinal anesthesia was initially successfully performed in all patients. Six patients required conversion to general anesthesia due to an inadequate block level (one in Group B and five in Group L, $P < 0.05$) and were therefore excluded (Figure 1).

A significant difference was found among the study groups when comparing the lengths of time needed to reach the T12 dermatome level and to reach the maximum sensory level ($P = 0.020$, $P = 0.041$, respectively). Reaching the T12 dermatome level took significantly longer in Group L than in Group B ($P = 0.006$). The length of time needed to reach the maximum sensory blockade was significantly longer in Group L than in Group LF ($P = 0.008$). The maximum sensory level of the side undergoing the operation was higher in the Group BF compared to Group B ($P < 0.05$). The sensory block regressed to the level of S2 in a shorter amount of time in Group L than in Group BF ($P = 0.049$) (Table 2).

Although there was no statistical difference between the groups, the motor blockade was not observed in 3 patients from Groups LF and L and 1 patient from Group

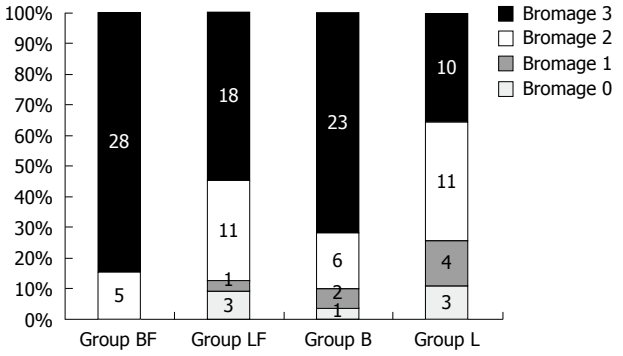

Figure 2 Maximal intensity of motor blockade expressed as a percentage of the population with definite motor block grade. 0 = No motor block; 1 = Inability to raise extended legs; 2 = Inability to flex knees; and 3: Inability to flex ankle joints. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine.

B. The intensity of the motor blockade was significantly higher in Group BF than in Groups LF and L and higher in Group B than in Group L ($P < 0.05$) (Figure 2). Complete recovery from the motor blockade occurred earlier in Groups LF and L than in Group BF and earlier in Group L than in Group B ($P < 0.05$) (Table 2).

A strictly unilateral sensory block (absence of detectable sensory block on the nonoperative side throughout the study period) was observed in 10 patients within Group BF (30%), 14 patients within Group LF (42%), 17 patients within Group B (53%) and 13 patients within Group L (46%) ($P = 0.30$). A strictly unilateral motor block (Bromage score = 0 on the nonoperative side throughout the study period) was observed in 20 patients within Group BF (60%), 24 patients within Group LF (72%), 23 patients within Group B (72%) and 23 patients within Group L (82%) ($P = 0.32$).

The time elapsed before micturition was significantly shorter in Group L than in Group BF ($P = 0.006$) (Table 2). Because of the inability to spontaneously void, four patients, one from each group, required urinary catheterization.

The time elapsed until VAS $\geq$ 4 was significantly longer in Group BF than in the other three groups and was significantly shorter in Group L than in Groups BF, LF, and B. There was no statistically significant difference between Groups LF and B (Table 2).

The time elapsed until the patient's discharge was significantly shorter in Groups B and L than in Group BF ($P = 0.021$, $P = 0.001$, respectively) (Table 2).

The quality of the block was significantly lower in Group L than in Groups BF, LF, and B ($P = 0.012$, $P = 0.003$, and $P < 0.001$, respectively). The requirement of additional sedation was greater in Group L than in the other groups. Patient satisfaction scores were significantly lower in Group L than on Groups BF and LF ($P = 0.039$). Surgeon satisfaction scores were significantly lower in Group L than in Groups BF, LF, and B ($P < 0.001$, $P < 0.001$, and $P = 0.024$, respectively) (Table 3).

Cardiovascular changes were unremarkable, and no statistically significant differences were found between the study groups regarding heart rate, mean arterial pressure, or hypotensive events. The occurrence of pruritus was significantly more frequent in patients receiving spinal fentanyl, and all cases resolved without treatment. Other side effects were not statistically different between the study groups (Table 4). None of the patients developed bradycardia or emesis in the postoperative period.

Table 3 Intraoperative and postoperative outcomes

Variables	Group BF (n = 33)	Group LF (n = 33)	Group B (n = 32)	Group L (n = 28)
Sedation	0	2	3	11[c]
Patient satisfaction (satisfied/unsatisfied)	33/0	33/0	28/4	24/4[a]
Surgeon satisfaction (satisfied/unsatisfied)	33/0	33/0	29/3	18/10[c]

Data shown are the mean ± SD, median (range) or count. [a]$P < 0.05$ compared with Group hyperbaric bupivacaine plus fentanyl (BF) and Group hyperbaric levobupivacaine plus fentanyl (LF); [c]$P < 0.05$ compared with Group BF, Group LF, and Group hyperbaric bupivacaine (B). L: Hyperbaric levobupivacaine.

Table 4 Frequency of adverse events n (%)

Adverse events	Group BF (n = 33)	Group LF (n = 33)	Group B (n = 32)	Group L (n = 28)	P value
Hypotension	2 (6)	2 (6)	0	0	0.289
Bradycardia	0	0	0	1 (4)	0.317
Emesis/vomiting	0	1 (3)	0	0	0.417
Shivering	6 (18)	5 (15)	7 (21)	6 (21)	0.894
Pruritus	11 (33)[a]	10 (30)[a]	0	1 (4)	< 0.001
Headache	4 (12)	7 (31)	6 (19)	4 (14)	0.754

[a]$P < 0.05$ compared with Group L and Group B. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine.

DISCUSSION

Our results suggest that 5 mg of hyperbaric bupivacaine and 5 mg of hyperbaric levobupivacaine plus 20 μg fentanyl provided spinal anesthesia of equivalent quality for patients undergoing outpatient arthroscopic knee surgery with unilateral positioning. However, the quality of the block was significantly lower in the group receiving 5 mg of levobupivacaine, and the time elapsed until discharge was significantly longer in the group receiving 5 mg of bupivacaine plus 20 μg of fentanyl.

The positioning of the patient during spinal anesthesia affects the distribution of the drug in the subarachnoid space and therefore affects recovery and discharge[11]. Patients who had received unilateral spinal anesthesia were ready to be discharged on average 42 min earlier than patients who received bilateral anesthesia[4]. Hyperbaric local anesthetic solutions have been often preferred over hypobaric and isobaric solutions in studies regarding unilateral spinal anesthesia. Hyperbaric bupivacaine is commercially available, but hyperbaric levobupivacaine requires the addition of dextrose to a

commercially available plain solution[12]. In the present study, hyperbaric levobupivacaine was obtained by adding glucose to isobaric levobupivacaine to achieve a unilateral spinal block. A recent review article suggested that 4-5 mg of hyperbaric bupivacaine can provide effective spinal anesthesia for knee arthroscopy[4]. Therefore, we compared 5 mg of hyperbaric bupivacaine with 5 mg of hyperbaric levobupivacaine in our study.

There are several studies comparing the properties of sensory and motor blocks with hyperbaric bupivacaine and levobupivacaine. Luck *et al*[6] reported that spinal anesthesia with 15 mg of hyperbaric bupivacaine and 15 mg of levobupivacaine achieve similar sensory and motor block characteristics in patients undergoing elective surgery. A study conducted by Erdil *et al*[13] compared the effectiveness of 7.5 mg of plain levobupivacaine with bupivacaine plus 15 μg of fentanyl in elderly patients. It was emphasized that the peak sensory block level was found to be significantly higher for bupivacaine than for levobupivacaine and that the length of time needed to reach the T10 sensory level was significantly longer for levobupivacaine than for bupivacaine. The authors suggested that levobupivacaine may not be quite as potent as bupivacaine[13]. In our study, the peak sensory block level was found to be higher for bupivacaine plus fentanyl. Moreover, the length of time needed to reach the T12 sensory block level was longer when using 5 mg of hyperbaric levobupivacaine than when using bupivacaine. Cappelleri *et al*[3] reported that injecting 5 mg of 0.5% hyperbaric levobupivacaine unilaterally was sufficient for short-lasting spinal blocks in patients undergoing outpatient knee arthroscopy[3]. In their study, an inadequate spinal block was observed in one patient receiving 5 mg of hyperbaric levobupivacaine, and none of the spinal blocks failed. However, in our study, sedation was required in eleven patients receiving 5 mg of hyperbaric levobupivacaine, and five patient blocks failed. The length of time required for complete resolution of the sensory block and the time elapsed until the patient was ready to be discharged were slightly longer in the those receiving 5 mg of levobupivacaine in our study compared to the study described above. In our study, the use of 5 mg of hyperbaric levobupivacaine led to fewer motor blocks and a longer time needed to attain a sensory block at the level of T12. These findings could have led to the increased number of patients requiring sedation.

Camorcia *et al*[14] found that spinal levobupivacaine was 29% less potent than bupivacaine in producing motor blocks. In our study, motor block quality and motor block regression time were found to be lower in the levobupivacaine groups than in the bupivacaine groups. Dobrydnjov *et al*[15] studied a restricted spinal block using 6 mg of hyperbaric bupivacaine with or without clonidine for inguinal hernia repairs. In their study, the authors reported a strictly unilateral spinal block in 47% of the patients. Cappelleri *et al*[3] reported a strictly unilateral motor block in 83% of patients who had received 5 mg of hyperbaric levobupivacaine. In our study, there were similar rates of strictly unilateral sensory and motor blocks to these studies.

The use of low dose local anesthetics while limiting the dose of the spinal block may result in an inadequate sensory block. For this reason, the addition of opioids to the local anesthetics can enhance the analgesia and prolong the sensory block without affecting the motor block[16]. Ben-David *et al*[17] demonstrated that the use of a diluted, low-dose bupivacaine is insufficient to provide spinal anesthesia, but the addition of 10 μg of fentanyl provides reliable anesthesia. We observed inadequate sensory and motor blocks in the group receiving 5 mg of hyperbaric levobupivacaine. However, our findings suggest that the quality of sensory and motor blocks is better when using 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl than when using 5 mg hyperbaric levobupivacaine alone.

Casati *et al*[18] reported that the unilateral technique with 8 mg of hyperbaric bupivacaine and 8 mg of hyperbaric levobupivacaine provided adequate spinal blocks for hernia repair procedures. Motor recovery was significantly faster after levobupivacaine, whereas the time elapsed until patient discharge was similar with both agents. Cappelleri *et al*[3] reported that the length of time required for the spinal block resolution and the time elapsed before discharge were shorter with 5 mg of levobupivacaine than with 7.5 mg of levobupivacaine. Although the time elapsed until the patient was discharged was slightly longer in the levobupivacaine group in our study compared to the study by Cappelleri *et al*[3], our results are not substantially clinically different.

Pruritus is a common complication arising from the use of intrathecal fentanyl[17]. Itching arises in 30%-33% of patients receiving 20 μg of fentanyl, and they recover without any treatment. The incidence of side effects such as hypotension and bradycardia is lower with unilateral spinal anesthesia than with conventional bilateral spinal anesthesia[4]. In our study, hemodynamic parameters were within safe ranges during the intraoperative and postoperative periods, and these side effects were observed in less than 4%-6% of the patients. We believe that these side effects are due to the low-dose intrathecal drug and the unilateral spinal block.

A common side effect of spinal anesthesia is urinary retention, which could be due to the fluid therapy used in the treatment of spinal anesthesia-induced hypotension or bilateral blockade of the parasympathetic plexus, which innervates the detrusor muscle. However, urinary retention occurs rarely in unilateral spinal blocks, since hemodynamic stability is better maintained and the function of the detrusor muscle has not been totally blocked[19]. Casati *et al*[18] reported no urinary retention after unilateral spinal anesthesia for inguinal herniorrhaphy. In our study, one patient in each study group complained of urinary retention, and they resumed spontaneous micturition after one catheterization. Moreover, it has been reported that dose-dependent spinal opioids influence bladder function and may cause urinary retention[19,20]. Liu

et al[2] reported that a 20 μg dose of fentanyl did not delay the ability to void. We also found no influence of the use of 20 μg of fentanyl in delaying the return of bladder function.

The main drawback associated with levobupivacaine is that the hyperbaric formulation is not available on the market. Diluting the hyperbaric formulation with dextrose for spinal anesthesia has a potential risk for infection. Furthermore, densities of solutions transformed into hyperbaric formulations can be different from the intended hyperbaric formulation. The density of the anesthetic solutions and the position of the patient are the most important factors affecting the intrathecal spread of the drug[4,12]. A limitation in our study is the fact that the density of levobupivacaine was not measured. However, in a laboratory investigation, McLeod showed that the density of levobupivacaine increases linearly with the addition of 8% dextrose[21].

In conclusion, both 5 mg of hyperbaric bupivacaine and 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl provided adequate and reliable anesthesia for arthroscopic knee surgery in the ambulatory setting. Both solutions provided a high level of patient and surgeon satisfaction without affecting the time elapsed until patient discharge, compared to 5 mg of hyperbaric bupivacaine plus 20 μg of fentanyl. In our opinion, 5 mg of hyperbaric levobupivacaine does not provide sufficient anesthesia for unilateral arthroscopic knee surgery.

COMMENTS

Background

Arthroscopic knee surgery is one of the most frequently performed ambulatory orthopedic surgeries. Spinal anesthesia is often preferred for lower extremity surgery in the ambulatory setting. For decades, lidocaine was the local anesthetic of choice for spinal anesthesia in ambulatory surgeries. However, its use is limited due to the risk of a transient neurological syndrome and neurotoxicity. Therefore, lower doses of long-acting local anesthetics have been used in outpatient surgeries. The comparison of low-dose hyperbaric bupivacaine to levobupivacaine with respect to the quality of the block and the time elapsed until discharge in outpatient knee arthroscopy procedures has not been investigated in the literature.

Innovations and breakthroughs

There are several studies comparing the properties of sensory and motor blockade in hyperbaric bupivacaine and levobupivacaine. This is the first study to compare hyperbaric bupivacaine with hyperbaric levobupivacaine in arthroscopic knee surgeries in the ambulatory setting. In this study, the dose and concentration of levobupivacaine used resulted in an inadequate block and higher sedation requirement for a greater number of patients compared to studies using hyperbaric levobupivacaine.

Applications

The study results suggested that, in knee surgeries in the ambulatory setting, 5 mg of hyperbaric bupivacaine provides a better spinal anesthesia than 5 mg of hyperbaric levobupivacaine. Equivalent spinal anesthesia, postoperative analgesia and recovery were attained with 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl without creating any adverse hemodynamic effects.

Terminology

Ambulatory surgery: Ambulatory surgery, also known as outpatient surgery, is surgery that does not require an overnight hospital stay. Unilateral spinal anesthesia: Unilateral spinal anesthesia consists of positioning the patient on the side that will undergo the operation for 10-15 min after the administration of the spinal anesthetic. Hyperbaric local anesthetic: Hyperbaric solutions are typically prepared by mixing the local anesthetic with 5% to 8% dextrose.

Peer review

The methodology of the investigation is sound and can support the outcome.

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CASE REPORT

Suspected cerebral arterial gas embolism during a laparoscopic Nissen fundoplication

Gaurav V Kulkarni, P Marco Fisichella, Barbara G Jericho

Gaurav V Kulkarni, P Marco Fisichella, Department of Surgery, Loyola University Medical Center and Hines Jr. VA Medical Center, Maywood, IL 60153, United States
Barbara G Jericho, Department of Anesthesiology, the University of Illinois Hospital and Health Sciences System, Chicago, IL 60612, United States
Author contributions: Kulkarni GV and Fisichella PM helped write the manuscript, participated in patient care, and approved the final manuscript; Jericho BG helped write the manuscript, critically reviewed the manuscript, and approved the final manuscript.
Correspondence to: Barbara G Jericho, MD, Department of Anesthesiology, the University of Illinois Hospital and Health Sciences System, 1740 W. Taylor Street, Room 3200, Chicago, IL 60612, United States. jericho@uic.edu
Telephone: +1-312-9964020 Fax: +1-312-9964019
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Abstract

We present the first case report known to us of a suspected cerebral arterial gas embolism (CAGE) leading to transient left-sided hemiparesis after a laparoscopic Nissen fundoplication. During the operation there was no evidence of hemodynamic compromise and the end-tidal carbon dioxide level and oxygen saturation had been within normal limits. Radiological studies and transesophageal echocardiography showed no abnormalities. We conclude that CAGE can occur during uncomplicated laparoscopic surgery even in the absence of demonstrable intracardiac shunts.

Key words: Paradoxical gas embolism; Arterial embolism; Laparoscopic Nissen fundoplication; Neurologic deficit; Laparoscopic surgery

Core tip: We present the first case report known to us of a suspected cerebral arterial gas embolism (CAGE) leading to transient left-sided hemiparesis after a laparoscopic Nissen fundoplication. During the operation there was no evidence of hemodynamic compromise and the end-tidal carbon dioxide level and oxygen saturation had been within normal limits. Radiological studies and transesophageal echocardiography showed no abnormalities. We conclude that CAGE can occur during uncomplicated laparoscopic surgery even in the absence of demonstrable intracardiac shunts.

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INTRODUCTION

Carbon dioxide (CO_2) embolism is a well-recognized complication during laparoscopic procedures utilizing CO_2 insufflation for the establishment of a pneumoperitoneum[1]. The clinical presentation of CO_2 embolism ranges from a complete lack of symptoms to neurologic injury, cardiovascular collapse or even death depending on the rate and volume of gas entrapment[2]. CO_2 embolism can be fatal, yet the incidence during laparoscopic surgeries is varied. The true incidence is difficult to determine secondary to subclinical cases and the sensitivity of the detection of gas embolism by available monitors during procedures. Hong *et al*[3] report that the incidence of subclinical embolisms in laparoscopic radical prostatectomies is 17%. Usually, venous embolism manifests in the first few minutes after the start of the gas insufflation during initial establishment of a pneumoperitoneum and it is due to inadvertent venous cannulation with a Veress needle or gas absorption through open venous channels. However, in many cases no noticeable hemodynamic changes are noted since the pulmonary circuit may filter

or reabsorb the small bubbles of CO_2 without causing any embolic obstruction[4]. Conversely, in the presence of intracardiac shunts, such as a patent foramen ovale or septal defect, the CO_2 embolus can reach the left side of the circulation resulting in varied degrees of neurologic or vascular deficits depending on the location where the embolus lodges[5]. Such paradoxical CO_2 embolisms are extremely rare events, especially in the absence of intracardiac shunts. Nevertheless, they could have disastrous consequences.

Herein, we present the first case known to us of a suspected cerebral arterial gas embolism (CAGE) in the absence of intracardiac shunts that led to a transient left-sided hemiparesis after an uncomplicated laparoscopic Nissen fundoplication.

CASE REPORT

A 22-year-old woman with gastroesophageal reflux disease unresponsive to maximal medical management and who failed lifestyle modifications was scheduled for a laparoscopic Nissen fundoplication. The patient also had a past medical history of Hashimoto's thyroiditis and Crohn's disease treated medically. Her past surgical history included two laparoscopic procedures: a bilateral ovarian cystectomy and a cholecystectomy, which had been uneventful. Four months prior to the laparoscopic Nissen fundoplication she had given birth to a healthy boy *via* a normal vaginal delivery.

The patient was brought to the operating room and standard American Society of Anesthesiologists noninvasive monitors (electrocardiogram, noninvasive blood pressure monitoring, oxygen saturation, capnograph, and temperature) were placed. After preoxygenation, the patient underwent a rapid sequence induction with propofol (200 mg) and succinycholine (100 mg) and the trachea was intubated. General anesthesia was maintained with air, oxygen, and sevoflurane. The patient was positioned with a beanbag on the operative table with both lower extremities placed in stirrups. Mechanical ventilation was adjusted to maintain the end-tidal CO_2 between 30-40 mmHg. The patient's abdomen was then prepped and draped. The Veress needle was inserted, a water drop test was performed, and the abdomen was insufflated at the rate of 3 L/min. The intra-abdominal pressure was built up to 18 mmHg according to recommendations set forth by Bhoyrul *et al*[6]. The introducer of the trocar was then removed and the laparoscope was reinserted into the abdominal cavity to inspect the entry area, ensuring that no intra-abdominal injuries were made upon entering the abdominal cavity. The patient was then placed in a sitting position to improve surgical exposure of the hiatus for the operation and the CO_2 insufflation pressure was decreased to 14 mmHg. The surgical and anesthetic course was uneventful. There were no episodes of sudden hypotension, bradycardia, arrhythmia, oxygen desaturation, or decrease in end-tidal CO_2 during the operation. The trachea was extubated without difficulty with the patient awake. In the recovery room, the nursing staff noticed the patient had a left eye ptosis and a left hemiparesis. A thorough neurologic assessment by a senior neurosurgeon in the recovery room demonstrated that the patient could not move her left upper arm and that she had 1/5 strength in her left lower extremity. Preoperatively, the motor strength in all extremities was 5/5. Deep tendon reflexes on the right were 2+ and were absent on the left side of the body. In addition to a diagnosis of possible CO_2 arterial embolism, our evaluation of this patient involved the differential diagnoses of a coagulopathy, intracardiac thrombus with subsequent embolus, cerebral vascular disease, and a hemorrhagic cerebral vascular event. A computed tomography (CT) scan was obtained within 1 h and showed no evidence of a stroke. The stroke team was informed and the patient was transferred by ambulance from the Veterans Administration Hospital to the University hospital in the immediate vicinity (one block away) for definitive care. Upon arrival to the emergency room (ER) of the University hospital, the patient was examined by the same surgical team who performed the laparoscopic procedure, by members of the stroke team, and by the ER attending physician. At this time, the patient had recovered the use of her left upper extremity to gain 3/5 strength and she had also improved her left lower extremity strength to 4/5. Motor strength on the right was unchanged at 5/5 and deep tendon reflexes on the right were 2+. Reflexes on the left side, which were initially absent, were found to be 1+.

A CT angiogram of the intracranial circulation failed to show any significant narrowing or obstruction to cerebral flow. Similarly, a hypercoagulable evaluation failed to show any hypercoagulable disorder. Finally, transesophageal echocardiography did not show any evidence of gas in any of the cardiac chambers or any demonstrable intracardiac shunt on color-flow Doppler imaging. The patient was admitted to the Neurological intensive care unit for monitoring and over a period 24 h she had complete resolution of her neurologic symptoms. She underwent a magnetic resonance imaging (MRI) on postoperative day two which was normal. Supportive treatment with postoperative pain control and fluid management were continued for the entire duration of the patient's hospital stay.

The patient was discharged on the third postoperative day with no residual weakness or deficits, tolerating a clear liquid diet without heartburn, regurgitation, or dysphagia. She was examined postoperatively at 2 wk and 2-mo follow-up in the Surgery and Neurology outpatient clinics. She continued to show no neurologic deficits. The patient has given written consent and has agreed to publication of this case report.

DISCUSSION

CAGE is an exceptionally rare event during laparoscopic surgery. The clinical presentation of CO_2 embolism varies with respect to the rate of entry of the gas and the size of the embolus, which can increase with the use of

nitrous oxide[7]. CO_2 embolus can result in "gas lock" with obstruction to right ventricular outflow, ventilation and perfusion mismatch, cardiac arrhythmias, pulmonary hypertension, and cardiovascular collapse. The diagnosis of a CO_2 embolism can be revealed by the auscultation of a millwheel murmur with a precordial or esophageal stethoscope, decrease in end-tidal CO_2 noted with capnography, increased end-tidal nitrogen, decrease in oxygen saturation by pulse oximetry, electrocardiographic changes, Doppler ultrasonography, transesophageal Doppler, and transesophageal echocardiography[8]. In addition to cardiopulmonary and neurological symptoms seen with CO_2 embolus, patients with CAGE may also experience seizures, headaches, dizziness, and visual field defects.

Radiologic evaluation is not always conclusive in the diagnosis of CAGE. CT scans can distinguish CAGEs from cerebral infarcts or hemorrhages; however, the distinction may be elusive[9]. MRI may show injured tissue with a fluid collection; yet, again, this is not reliable especially if the patient has mild symptoms[10].

The treatment of CAGE is similar to the treatment of a CO_2 embolus. However, the treatment of a patient with CAGE may include the transfer to a hyperbaric oxygen chamber if the patient is stable; placing the patient in the supine position; anticonvulsant medications; and lidocaine[11]. Furthermore, distinct from the treatment of venous gas embolism in which the patients are placed in the Trendelenburg and left lateral decubitus position, patients with CAGE should be placed in the supine position to avoid gas bubbles flowing toward the head and to prevent cerebral edema[12]. However, under general anesthesia with stable cardiopulmonary signs, small cerebral arterial emboli may go undetected until neurological signs are apparent after the emergence from anesthesia, as we encountered in this patient.

The exact cause of CAGE in this case remains unknown. The rapid elimination of CO_2 due to the high solubility of CO_2 in blood as well as a reduction in CO_2 insufflation pressures contributed to the transient nature of this patient's symptoms and the elusiveness of medical studies. The blood/gas solubility of CO_2, nitrous oxide, dissolved oxygen, and nitrogen are 0.60, 0.45, 0.024, and 0.013 mL/mL solvent with 100% gas at 17 degrees Celsius respectively. Furthermore, since the blood solubility of nitrous oxide and CO_2 are similar, discontinuing nitrous oxide will not reduce the size of a CO_2 embolus as it would an air embolus[13].

Intraoperatively, a more urgent intraoperative transesophageal echocardiogram would have been indicated in the setting of hemodynamic compromise[14]. Such a hemodynamic collapse did not occur in this patient perhaps because, as shown by Huang *et al*[15], the gas was released in time without formation of a fatal pulmonary gas lock. Although during the operation we had no evidence of bleeding or vascular injury due to the placement of the Veress needle, we postulate that the initial intra-abdominal pressure of 18 mmHg might have been high enough for the CO_2 to enter and bypass the pulmonary circuit and that, at the same time, was kept brief enough to avoid a pulmonary gas lock. In fact, Eiriksson *et al*[16] demonstrated that high intra-abdominal pressures (16 mmHg) during experimental laparoscopic liver resection in swine reduced bleeding but increased the risk of gas embolism.

Paradoxical embolisms have been demonstrated in patients without intracardiac defects. Bedell *et al*[17] presented a case of a patient in the sitting position undergoing occipital artery to posterior inferior cerebellar artery bypass who developed paradoxical gas embolism in the absence of any intracardiac defect. Bedell *et al*[17] demonstrated transesophageal echocardiographic evidence for the transpulmonary passage of gas from the right to the left side of the circulation. The event confirmed the validity of a 50-year-old theory that attributed a precise pathogenic role to arteriovenous connections, called "*sperrarteries*", within the pulmonary vasculature. According to this theory, the *sperrarteries* bypassed the pulmonary parenchyma and were thought to serve as rapid conduits for absorbed venous air to travel to the arterial side of the circulation[18].

In conclusion, we report, to our knowledge, the first case of suspected CAGE occurring during a laparoscopic Nissen fundoplication causing transient neurologic symptoms. We conclude that CAGE can occur during uncomplicated laparoscopic surgery even in the absence of demonstrable intracardiac shunts and that such an event might be prevented by keeping the CO_2 insufflation pressure set at 15 mmHg with a slow flow rate during the creation of the pneumoperitoneum[19].

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CASE REPORT

Fractured tracheostomy tube obturator: A rare cause of respiratory distress in a tracheostomized patient

Mussarat Afzal, Hadi Al Mutairi, Ikram Chaudhary

Mussarat Afzal, Hadi Al Mutairi, Ikram Chaudhary, King Fahad Specialist Hospital, Dammam, PC 31444, Eastern Province, Saudi Arabia
Author contributions: All authors contributed to this work.
Correspondence to: Dr. Mussarat Afzal, Consultant Anesthetist, King Fahad Specialist Hospital, PO Box 15215, Dammam, PC 31444, Eastern Province,
Saudi Arabia. dr_mussarat_a@hotmail.com
Telephone: +966-56-1116907 Fax: +966-56-1116907
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Abstract

Foreign body aspiration is a worldwide health problem which often results in life threatening complications. Tracheostomy tube fracture resulting in airway obstruction is a serious condition which has been reported in the medical literature. We report a rare case of a tracheostomy obturator fractured and lodged in tracheobronchial tree in a patient who presented with acute respiratory distress. Rigid or flexible bronchoscopy is frequently necessary for the diagnosis as well as the treatment. In adults, removal of the foreign body can be attempted during a diagnostic examination with a fiberoptic bronchoscope under lignocaine local infiltration with sedation, which may help to avoid any further invasive procedures. Flexible bronchoscopy should always be considered in foreign body aspiration. A periodic review of the techniques of tracheostomy care, including timely check-ups for signs of wear and tear, can possibly eliminate such avoidable late complications.

Key words: Respiratory distress; Tracheostomy; Foreign body; Aspiration; Bronchoscopy

Core tip: Foreign body aspiration is often a serious medical condition that demands timely recognition and prompt action. Delayed diagnosis and subsequent delayed treatment is associated with serious and sometimes life threatening complications. We describe a case of acute respiratory distress following aspiration of part of the obturator of a tracheostomy tube during a routine change of the tracheostomy tube.

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INTRODUCTION

Foreign body aspiration is often a serious medical condition that demands timely recognition and prompt action. Delayed diagnosis and subsequent delayed treatment is associated with serious and sometimes fatal complications[1]. In adults, however, foreign body aspiration can be tolerated and remain undetected for a long time. We describe a case in which part of the tracheostomy obturator was broken and migrated into the tracheobronchial tree, resulting in acute respiratory distress.

CASE REPORT

A tracheostomized 68-year-old male known to have hypertension and diabetes presented at our emergency room with progressive acute respiratory distress. During a routine change of the tracheostomy tube, medical staff noticed that the tracheostomy obturator was fractured and had migrated into the trachea. The bronchoscopic removal in a referral hospital was unsuccessful. Therefore, the patient was referred to our hospital for further management. Past medical history revealed that the patient had had a cardiac arrest 3 mo earlier due to myocardial ischemia and was successfully resuscitated. After

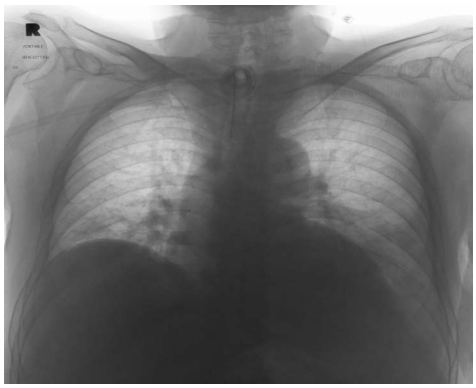

Figure 1 The prominent broncho-pulmonary markings without a radio-opaque foreign body in the right lung.

prolonged cardiopulmonary resuscitation, the patient remained on a ventilator for 3 wk. Thus, the tracheostomy was done after the few unsuccessful attempts of weaning from the ventilator. Pre anesthesia evaluation revealed electrocardiography (ECG) showing periodical supra ventricular tachycardia with antero-lateral ischemic changes, whereas the echocardiography showed a moderately dilated left ventricle with severely impaired systolic function, with an ejection fraction of 10%-25%.

His computed tomography of the brain showed an old infarct and microangiopathic ischemic change. His respiratory rate was 35/minute, O_2 saturation 88%-89% and blood pressure 90/50 mmHg. He was conscious and oriented but both his upper and lower limbs were spastic. Auscultation of the chest revealed decreased breath sounds on the right side. A subsequent X-ray of the chest did not show any foreign body (Figure 1). He was immediately taken to the operating room.

After putting on ECG leads, pulse oximeter, oxygen through a face mask and noninvasive blood pressure measurement, Xylocaine 2% was infiltrated into the trachea through the tracheostomy tube. About 1 mg of Midazolam was given intravenously and 15 mL/h propofol infusion was commenced.

The fiberoptic bronchoscopy revealed a fractured part of the obturator deeply lodged in the right bronchus (Figure 2A). After suction of secretions, the obturator was removed with endoscopic forceps and it was pulled out from the tracheostomy tube with artery forceps (Figure 2B). After the uneventful procedure, the patient was sent to the recovery room. Two days later, the patient was referred back to the primary hospital for long term management.

DISCUSSION

The first case of a fractured, metallic tracheostomy tube was reported by Bassoe *et al*[2] in 1960. Since then, this kind of a complication has been published in the medical literature frequently, with all kinds of tracheostomy tubes (TT). The composition of TTs range from metal, poly vinyl chloride to silicone[3]. A number of factors predispose fracture of one of the flanges of the TT. The most frequent weak points of TT are the junctions between

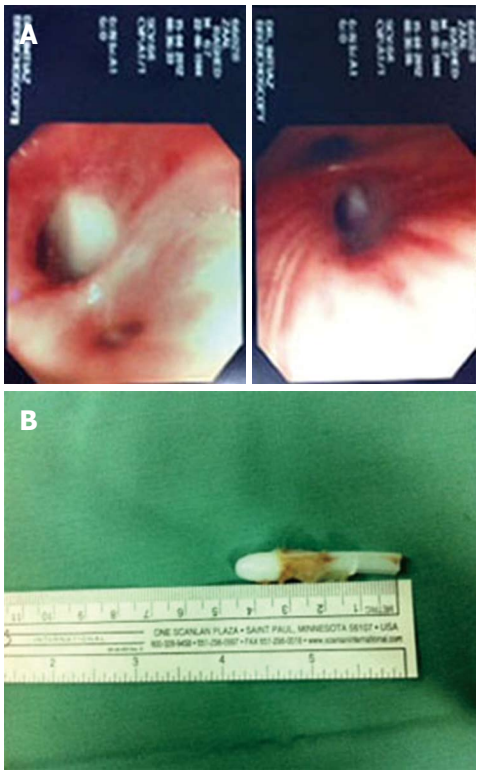

Figure 2 Bronchoscopic view showing the tracheostomy tube obturator lodged in the right main stem bronchus (A) and a tracheostomy obturator after removal from the right main bronchus (B). The length of the broken obturator measures 4.5 cm.

the tube and the neck plate, the distal end of the tube and the fenestration site[4,5]. In our case, it was not the TT but part of the obturator (introducer) which fractured and migrated to the distal trachea and was noticed during a routine change of tracheostomy tube by the staff.

Foreign body aspiration can be a life-threatening emergency. An aspirated solid or semisolid object may lodge in the larynx or trachea. If the object is large enough to cause nearly complete obstruction of the airway, asphyxia may rapidly lead to death[6].

Tracheobronchial foreign body (TFB) aspiration is rare in adults, although the incidence rate rises with advancing age. Risk factors for TFB aspiration in adults are a depressed mental status or impairment in the swallowing reflex[5]. Symptoms associated with TFB aspiration may range from cough, dyspnea, fever and acute asphyxiation with or without complete airway obstruction. In adults, many other medical conditions mimic breathing abnormalities similar to those associated with TFB aspiration. In our case, there was a definitive history of a missing part of the obturator during a change of the TT.

If the history is not suggestive, then only a high index of suspicion can ensure proper diagnosis and timely removal of the foreign body[6]. Initial treatment is airway management. Radiographic imaging may assist in localizing the foreign body. Bronchoscopic removal of the foreign body is necessary to avoid long-term sequelae. Flexible bronchoscopy is effective both in the diagnosis and removal of foreign bodies[7].

Almost all aspirated foreign bodies can be extracted bronchoscopically. If rigid or flexible bronchoscopy is unsuccessful, surgical bronchotomy or segmental resection may be necessary. Chronic bronchial obstruction with bronchiectasis and destruction of lung parenchyma may require segmental or lobar resection.

A pulmonologist or thoracic surgeon with experience in foreign body extraction should immediately perform bronchoscopic inspection and extraction of the object[8].

An anesthesiologist may be needed to maintain adequate ventilation and control of the upper airway during diagnostic and therapeutic procedures. Rigid bronchoscopy is performed with the patient under general anesthesia or heavy sedation[8].

As foreign bodies in the TBT are uncommon in adults, the clinician must be vigilant regarding their possibility. Foreign body aspiration should be considered especially in the etiology of recurrent lung diseases and in the presence of risk factors for aspiration, in particular with different neurological and neuromuscular diseases. They can be safely and successfully removed in the majority of patients by using fiberoptic bronchoscopy under local anesthesia alone or under local anesthesia with sedation. An endotracheal intubation is recommended in cases of a repeated procedure.

An intermittent review of the techniques of tracheostomy care should be done, including timely check-ups for signs of wear and tear which can possibly eliminate such avoidable late complications[9].

Since there are no universally accepted and published standards of care for a tracheostomy tube, the policy should be to provide patients who require an indwelling tracheostomy tube with the following recommendations for home care: (1) Replace the tracheostomy tube every 6 mo; (2) Change/clean the inner cannula every 48 h; (3) Replace the tracheostomy ties weekly; (4) Change the dressing daily; and (5) Use nocturnal humidification[10].

In conclusion, cases of tracheostomy tube fractures and aspiration into TBT have been reported in the literature. We, hereby, report a rare case of the TT obturator that had fractured and migrated to the right main stem bronchus. Proper care and high vigilance when the obturator is removed during suction and cleaning of the TT is of high clinical importance.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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