ORIGINAL ARTICLE

A randomized prospective study of BIS guided low-flow sevoflurane anesthesia; is air safer than nitrous oxide?

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ABSTRACT

Objective: This prospective randomized BIS controlled study was conducted to compare low-flow anesthesia (LFA) techniques with or without nitrous oxide (N_2O) using remifentanil and sevoflurane, with respect to ventilation parameters and sevoflurane consumption.

Methodology: Forty-five, ASA I/II women younger than 65-year-old, scheduled for gynecological surgery lasting nearly two hour under general anesthesia were enrolled. Electrocardiogram (ECG), pulse oximetry, non-invasive arterial pressure, train-of-four (TOF) and bispectral index (BIS) were monitored. Anesthesia was induced by inj propofol 2 mg/kg with increments of 10 mg until BIS was under 60 and rocuronium 0.6 mg/kg. Patients were randomized to one of three groups, 15 patients in each, to receive either N_2O (Group-N) or N_2O-free anesthesia (Groups RI nd RII). All groups received bolus remifentanil 0.5 μg/kg and then infusions @ 0.2 μg/kg/min (Group-R I), or 0.05 μg/kg/min (Group-R II) as maintenance. Anesthesia was maintained with sevoflurane in O_2 + N_2O or air. Signs indicating adequate depth of anesthesia during maintenance phase of anesthesia were HR, arterial blood pressure and BIS. The goal was to obtain a BIS value between 40 and 60 and hemodynamic parameters within 20% of baseline values. Opioid infusions were constant as sevoflurane vaporizer dial setting was adjusted in ± 0.5% volumes to maintain this goal. Systolic, diastolic and mean arterial pressures, HR, SpO_2, the inspired and expired gas partial pressure measurements of O_2, sevoflurane, N_2O, and CO_2, BIS values sevoflurane vaporizer dial settings, and recovery times were recorded. Measuring points were at every 5 min during surgery. A minimum inspired oxygen concentration (FiO_2) of 0.3 was maintained. Consumption and costs for sevoflurane were calculated.

Results: Demographic data, duration of surgery and anesthesia were similar between the groups. A significant decrease was observed in FiO_2 by time in all groups. For all recording times FiO_2 was statistically greater in Group-N. The difference between delivered O_2 and FiO_2 was the lowest in Group-N. The difference between inspired and expired fractions of sevoflurane (Fi_{sevo} and Fet_{sevo}) reduced by time during the low flow period. It was lower in Group-N than in remifentanil groups. Total sevoflurane consumption was significantly greater in Group-R II than Group-N but there was no significant difference in sevoflurane consumption and costs per patient per minute between groups. Recovery times were comparable between the groups.

Conclusions: We concluded that risk of hypoxia and volatile anesthetic consumption did not differ with or without N_2O in remifentanil-sevoflurane, low flow anesthesia. Monitoring FiO_2 is essential in both air/O_2 and N_2O/O_2 mixtures. Both are safe to administer unless FiO_2 is lower than 30%. BIS-guided sevoflurane with its low solubility feature successfully adapts quickly to variable anesthetic depth levels during low-flow anesthesia.

Key words: Anesthesia; Closed Circuit, Anesthesia; Rebreathing; Nitrous oxide; Consciousness Monitors; Bispectral Index Monitor

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INTRODUCTION

There is a debate on N_2O usage whether it is a unique or an outdated drug;[1,2] and compelling arguments have been presented to question its continued use as a carrier gas in anesthesia.[3-6] When N_2O is not present in anesthesia, an air/O_2 mixture is frequently used as the prolonged use of 100% O_2 has its own disadvantages.[7]

Other than general concerns about N_2O in standard anesthesiology practice, when it comes to the low flow anesthesia (LFA) technique, questioning its ongoing usage gains importance.[8] Low-flow techniques using O_2/N_2O mixtures have been well studied[9] than the use of air/O_2 mixtures. Should we then assume air is safer in LFA? Nitrous oxide has favorable features and possible advantages as an amnesic in the prevention of intraoperative awareness.[3] European Society of Anaesthesiology task force recently concluded that when not specifically contraindicated N_2O could be used.[10] Hendrickx et al revised pharmacokinetic and pharmacodynamic concepts of inhaled anesthetics including nitrous oxide and suggested that the second gas affect of N_2O may be more pronounced than assumed.[11]

This study hypothesized that omitting N_2O from carrier gas compositions would help to utilize LFA technique and would be useful as an academic demonstration of inhalational anesthetic pharmacokinetics and pharmacodynamics, yet its impact on cost-effectiveness was unknown. Primary outcomes were the changes of delivered, inspired and expired gas partial pressure measurements of O_2, sevoflurane, N_2O, and CO_2 during LFA with and without N_2O. Additional outcomes included the comparison of the effects of different remifentanil doses with nitrous oxide on recovery times as well as volatile anesthetic consumption and cost under BIS monitoring.

METHODOLOGY

This prospective, randomized study was conducted on 45, ASA I/II women under 65 years old, who were scheduled for gynecological surgery of approximately two hours duration under general anesthesia. Institutional Ethics Committee approval and written informed consent from each subject were obtained. The exclusion criteria were a previous unusual response to anesthetics, emergency surgery, a history of hepatic, renal or significant cardiovascular disease, history of alcohol or drug abuse, and procedures with an expected duration of less than 30 min.

No premedication was given. Anesthesia was administered and anesthetic gases monitored with Julian™ (Dräger Medizintechnik, Lübeck, Germany) anesthesia machine. Before each anesthetic administration, fresh soda lime with new respiratory tubing and connections were used.

Routine monitoring included electrocardiogram (ECG), pulse oximetry (SpO_2), non-invasive mean arterial pressure (MAP). Additionally, bispectral index (BIS) monitoring (BIS XP Platform, Aspect Medical Systems Inc., Newton, USA) was used. The bispectral values were monitored continuously from before the induction until the patient fully recovered after surgery. Neuromuscular transmission was monitored by train-of-four nerve stimulation (TOF, Innervator NS 252, Fisher & Paykel Electronics Ltd., Auckland, New Zealand).

In all patients, following 5 min of preoxygenation with 100% oxygen, anesthesia was induced by propofol 2.0 mg/kg IV with increments of 10 mg until the BIS was under 60. A neuromuscular block was administered with inj rocuronium 0.6 mg/kg. Patients were randomly placed into one of three groups containing 15 patients each, by means of a computer-generated table of random numbers designating a N_2O group (Group-N), or two N_2O-free groups (Groups RI and RII). All of the groups received remifentanil 0.5 μg/kg as a loading dose. Continuous infusions were maintained @ 0.2 μg/kg/min (Group-R I) or @ 0.05 μg/kg/min (Group-R II) in remifentanil groups. Anesthesia was maintained with sevoflurane/oxygen/N_2O in Group-N and with sevoflurane/oxygen/air in Groups RI and RII. Fresh gas flows were supplied with 6.0 L/min during the first five minutes, than adjusted to 1.0 L/min with a sevoflurane vaporizer setting of 2% and 2.5% respectively. Opioid infusions were constant as the sevoflurane vaporizer dial setting was adjusted in ± 0.5% volumes to maintain BIS 50 ± 10. Incremental doses of 0.01 mg/kg rocuronium were given at two twitches achieved with a train-of-four stimulus. End-tidal carbon dioxide, tidal volume and respiratory rate were adjusted to 30-35 mmHg, 8 ml/kg and 8-12/min respectively.

Systolic, diastolic and MAPs, heart rate (HR), SpO_2, the inspired and expired gas partial pressure measurements of oxygen, sevoflurane, N_2O, and CO_2, BIS values were recorded before induction, and at 5-minute intervals thereafter throughout the study. Delivered gas concentrations (oxygen, sevoflurane) were defined as the gas concentrations set at the anesthesia machine and vaporizer and inspired fractions (Fi) and expired fractions (Fet) of

oxygen, sevoflurane, N_2O, and CO_2 were measured from the breathing system.

In case of a decrease in inspired O_2 concentration ($FiO_2 < 0.3$) or in peripheral oxygen saturation ($SpO_2 < 94$), it was planned that an increase in O_2 flow by 10% of the total flow and a decrease of N_2O/air by the same rate would be carried out. Hemodynamic stability was maintained by adjusting the inspired anesthetic concentration. If the MAP increased by > 20% of the baseline value, the anesthetic gas vaporizer volume was increased by 0.5%. When HR and MAP were < 20% of the baseline, the anesthetic gas concentration was decreased by 0.5%. If this did not prove effective to treat hypotension, 5-10 mg ephedrine was given IV.

Before completion of the last skin sutures, the vaporizer was turned off, fresh gas flow was increased to 4 L/min, and ventilation was performed manually with 100% O_2. Residual muscle paralysis was reversed with neostigmine administration. The durations of anesthesia and surgery were noted. The response times by 'eyes opening' on command, and being well-oriented in time and place, were recorded. Extubation was done when they successfully responded to the command to open their eyes. The time between cessation of the inhalation anesthesia and extubation was noted. A postanesthetic recovery score was evaluated at 10th and 30th minutes after extubation according to the Aldrete Recovery Scoring System in the postanesthesia care unit. Patients who had a score over nine were transported to the ward. Consumption and costs for sevoflurane were calculated by use of the Dion Formula.[12]

The statistical analysis was performed with SPSS 15.0 software for Windows (IBM, USA). All data are expressed as mean ± standard deviation (Mean ± SD). *P* values <0.05 were considered statistically significant. One-way analysis of variance or the Kruskal-Wallis tests were used for between-group comparisons. Analysis of variance was used for repeated measures of intergroup comparisons.

RESULTS

The study included 45 women of ASA I-II physical status, between the ages of 41-65 years. Demographic variables were similar between the groups (Table 1). The mean anesthesia duration was 95.27 min for Group-N, 100.27 min for Group-R I, and 104.07 min for Group-R II ($p > 0.05$).

There was a significant decrease in HR and MAP after induction in all groups. Remifentanil groups revealed no hemodynamic response to intubation, whereas in Group-N, there was a significant increase in MAP. During the low flow period, HRs were significantly lower than baseline values in all groups and MAPs also decreased in remifentanil groups without statistical differences between groups.

The difference between delivered O_2 and FiO_2 was the lowest in Group-N compared with the remifentanil groups (Table 2). A significant decrease was observed in FiO_2 by time in all groups. For all recording times, FiO_2 was statistically greater in Group-N ($p < 0.05$). The lowest FiO_2 % monitored in each group was 38% for Group-N, 32.73% for Group-R I, and 34.47% for Group-R II (Table 3).

For maintaining constant BIS values (40-60), delivered sevoflurane volume was similar between the groups. The difference between inspired and expired fractions of sevoflurane (Fi_{sevo} and Fet_{sevo}) reduced by time during the low flow period. It was mostly lower in Group-N than in remifentanil groups (Table 4).

Total consumption of sevoflurane was significantly greater in Group-R II than in Group-N [36.71 ± 7.46 vs. 28.93 ± 6.28 ml] but there was no significant difference in sevoflurane consumption and cost per patient per minute between groups.

Recovery times were comparable between the groups (Table 1). The Aldrete recovery scores were also similar in PACU. Patients were recorded with an Aldrete score over 9 after 7.9 ± 5.9 min in Group-N, 8.1 ± 6.3 min in Group-R I and 8.3 ± 6.7 min in Group-R II ($p > 0.05$).

DISCUSSION

Omitting N_2O was suggested to have a number of advantages in LFA practice. In the present study, a significant decrease was observed in FiO_2 by time for all groups. At all recording times, the difference between delivered O_2 and FiO_2 was the lowest in N_2O group compared with remifentanil groups. None of the study groups led to hypoxic gas mixtures with FiO_2 over 30%.

LFA techniques optimize the performance of re-breathing systems since high fresh gas flows minimize rebreathing fractions of exhaled gases.[9] With technological advances in modern anesthesia, machines equipped with inhaled and exhaled gas monitoring permits safe and efficient usage of low flow techniques, especially when new inhalational anesthetics with low tissue solubility are administered.[12,13]

Table 1: Patient demographics, duration of anesthesia and operation, and recovery features (n, mean ± SD)

Variables	Group-N	Group-R I	Group-R II
ASA (I/II)	11/4	7/8	7/8
Age (yrs)	50.07 ± 6.58	48.53 ± 4.82	49.53 ± 6.52
Height (cm)	160 ± 6	160 ± 4	160 ± 6
Weight (kg)	69.87 ± 13.01	74.60 ± 14.16	78.60 ± 14.06
Duration of surgery (min)	85.73 ± 17.27	90.53 ± 22.57	97.27 ± 22.66
Duration of anesthesia (min)	95.27 ± 17.79	100.27 ± 23.84	104.07 ± 22.25
Eye opening time (min)	3.8 ± 1.47	5.2 ± 2.48	4.07 ± 2.09
Extubation time (min)	5.33 ± 1.92	6.07 ± 2.52	5.93 ± 2.12

Table 2: Disparity between the oxygen concentrations set at the anesthesia machine (delivered oxygen) and in the breathing system (inspired oxygen concentration - FiO_2) (mean ± SD)

Time	Group-N	Group-R I	Group-R II
4 L	3 ± 2.04*†	8.2 ± 3.1	6.8 ± 3.71
1 L 5min	4 ± 1.96*†	11.93 ± 2.05	10.93 ± 2.49
1 L 15min	7 ± 1.31#*†	15 ± 2.48#	14.93 ± 2.37#
1 L 30min	10 ± 1.13#*†	16.4 ± 2.61#	15.53 ± 3.14#
1 L 45min	11.47 ± 1.13#*†	16.87 ± 2.67#	15.27 ± 3.37#
1 L 60min	12 ± 1.77#*†	17.27 ± 3.77#	15.2 ± 3.28#

*p<0.05 (compared with Group-R I),
†p<0.05 (compared with Group-R II),
#p<0.05 (compared with 1 L 5 min)

Table 3: Changes in FiO_2 by time (mean ± SD)

Time	Group-N	Group-R I	Group-R II
4 L	47 ± 2.04*†	41.8 ± 3.1	43.2 ± 3.71
1 L 5min	46 ± 1.96*†	38.07 ± 2.05	39.07 ± 2.49
1 L 15min	43 ± 1.31#*†	35 ± 2.48#	35.07 ± 2.37#
1 L 30min	40 ± 1.13#*†	33.6 ± 2.61#	34.47 ± 3.14#
1 L 45min	38.53 ± 1.13#*†	33.13 ± 2.67#	34.73 ± 3.37#
1 L 60min	38 ± 1.77#*†	32.73 ± 3.77#	34.8 ± 3.28#

*p<0.05 (compared with Group-R I),
†p<0.05 (compared with Group-R II),
#p<0.05 (compared with 1 L 5 min)

Table 4: The difference between inspired (Fi_{sevo}) and expired (Fet_{sevo}) fractions of sevoflurane (mean ± SD)

Time	Group-N	Group-R I	Group-R II
4 L	0.23 ± 0.06*†	0.35 ± 0.07	0.37 ± 0.08
1 L 5min	0.19 ± 0.06*†	0.26 ± 0.05	0.27 ± 0.07
1 L 15min	0.18 ± 0.06*†	0.25 ± 0.06	0.26 ± 0.07
1 L 30min	0.12 ± 0.09#*†	0.21 ± 0.06#	0.23 ± 0.1#
1 L 45min	0.11 ± 0.07†	0.13 ± 0.11#	0.19 ± 0.05#
1 L 60min	0.09 ± 0.08#	0.1 ± 0.18#	0.13 ± 0.14#
1 L end	0.05 ± 0.21#	0.05 ± 0.12#	0.08 ± 0.09#

*p<0.05 (compared with Group-R I)
†p<0.05 (compared with Group-R II)
#p<0.05 (compared with 1 L 5 min)

With low-flow techniques at reduced fresh gas flows, the fraction of expired gases in inspired gas concentrations increases and a disparity between the gas concentrations set at the anesthesia machine and in the breathing system develops. Rebreathing increases and O_2 concentrations accordingly reduce in the exhaled gases, inspired O_2 becomes lower than the delivered O_2 concentration, and thus a risk of hypoxia occurs.

In an earlier randomized clinical study, Hendrickx et al examined the effect of different air-O_2 mixtures and fresh gas flows on the relationship between the delivered and inspired O_2 in a circle system.[15] In accordance with our findings, they found a significant difference especially in the utilization of air-O_2 mixtures with fresh gas flows under 2 L/min. They reported that the oxygen concentration in the exhaled gases decreases and the nitrogen concentration increases due to nitrogen accumulation. The authors concluded that more oxygen should be added when air-oxygen mixtures are administered in flow rates of less than 2 L/min to maintain the desired FiO_2. In Bozkurt's study of N_2O-free LFA in children, despite the statistically significant decrease in inspired oxygen concentration, the high-delivered oxygen concentration (60%) prevented the occurrence of hypoxic gas mixtures.[16] We also preferred 50% O_2 to prevent the possibility of

hypoxemia. For all these reasons, analysis of the FiO_2 is mandatory when using air or N_2O with LFA.

Similar to changes in oxygen concentration, the use of a fresh gas flow of 1 L/min decreases the inspired and expired values of inhaled anesthetic gases compared with the vaporizer settings. Johansson et al investigated the effect of two different fresh gas flows on inspired and end-tidal sevoflurane concentrations with a fixed vaporizer setting and noted a significant difference between 1 and 2 L/min for inspired and end-tidal concentrations.[17] Using a 1 L/min fresh gas flow and a 2% vaporizer setting of sevoflurane, these authors found that the inspired and end-tidal sevoflurane concentrations in adult patients after 30 min of LFA were 1.4% and 1.2% respectively, while after 120 min of anesthesia they were approximately 1.5% and 1.3%. With the same fresh gas flow and vaporizer setting, Bozkurt et al demonstrated a similar significant decrease in the inspired and end-tidal value of sevoflurane compared with the vaporizer setting.[16] Park et al also showed the same effect of low fresh gas flow on isoflurane concentrations at constant vaporizer settings.[18] In the current study, delivered sevoflurane was not fixed to a constant concentration; alterations in vaporizer settings were adjusted to maintain a BIS value of 40-60. But in line with the literature findings, inspired and expired sevoflurane concentrations differed from the vaporizer settings. With constant BIS values (40-60), sevoflurane vaporizer settings were similar between the groups. The differences between the delivered sevoflurane volume and the end-tidal sevoflurane as well as inspired and expired fractions of sevoflurane (Fi_{sevo} and Fet_{sevo}) were also evaluated and both decreased in time during low flow period. These differences were mostly lower in the N_2O group than the remifentanil groups.

Remifentanil as a selective mu-opioid receptor-agonist provides optimal analgesia without producing a delay in recovery. The metabolism of remifentanil is independent of liver and kidney functions and it is distinguished by non-specific esterase in blood and tissue. Its short half-life is independent of the administered dose and duration of administration.[19] The absence of analgesic effect in nitrous oxide-free groups in the present study was prevented by remifentanil infusions. We evaluated more stable and controllable hemodynamic parameters in remifentanil groups clinically but they were not statistically significant.

Due to the low solubility and high concentration delivered by the vaporizer, sevoflurane enables a safe and convenient control of the anesthetic level and is especially suitable for LFA in clinical practice. Moreover, the use of sevoflurane was suggested to be more economical and ecologically efficient only by LFA.[17] At low fresh gas flows, the price difference for 1 MAC-hour expands for the volatile anesthetics with low solubility.[20]

In clinical practice, while carrying out nitrous oxide-free LFA, utilizing opioids can compensate the insufficient analgesic effect. Furthermore, when it comes to omitting N_2O, awareness might be an issue of concern. The approach to light anesthesia in the LFA technique is to increase the volatile anesthetic concentration by 0.2-0.25×MAC or the FGF rate for a certain period.[8] LFA is less costly but it provides less control of the depth of anesthesia. This means that the potential risks of light anesthesia or overdosing during LFA are greater than high flow techniques, so the monitoring of anesthetic agents and appropriate control of vaporizers are necessary during LFA.[18,20,21] End tidal volatile anesthetic concentrations and minimum alveolar concentrations have been mostly used as a measure to maintain an adequate anesthetic level. In the present study, alterations in FGF were not permitted but the depth of anesthesia was controlled by changing vaporizer setting via BIS monitoring. The benefits of LFA when combined with the measurement of the depth of the anesthesia were considered in order to reduce volatile anesthetic consumption while avoiding risk of awareness. However, total consumption of sevoflurane was calculated to be significantly less in the N_2O group than in the low remifentanil regimen group. There was no significant difference between the N_2O group and the other remifentanil group. Presumably, in the lower remifentanil group, a single dose of remifentanil was insufficient for meeting analgesia. Similar with our findings, in another study that evaluated drug consumption related to variations in the fresh gas flow with the use of nitrous oxide at 1 MAC sevoflurane, sevoflurane utilization was found lowest at nitrous oxide in the oxygen group even compared with the lowest FGF oxygen in air group.[22] Jakobsson et al also demonstrated that with fresh gas flow set at 3 L/min, the use of nitrous oxide decreased the sevoflurane cost by about 60% and the cost associated with the inhaled anesthetic by 40%.[23]

In an earlier study, Hendrickx concluded that during minimal flow anesthesia, the vaporizer setting required for maintaining a constant Fet_{sevo}, was lower with an O_2-N_2O mixture than when 100%

oxygen was used. This is probably due to the fact that when using O_2-N_2O as the carrier gas, less gas and vapors are wasted.[24] In a later study, the same authors identified a second gas effect of N_2O on sevoflurane.[25]

Bispectral index monitoring has been suggested not only to improve the financial burdens of anesthesia but also for the recovery profile when compared to the results of patients not monitored with BIS[24]. However, in the present study, recovery times as well as Aldrete Recovery Scores were comparable between the groups.

LIMITATIONS

One of the limitations of this study was small patient population and lack of sample size estimation. Also, a more extensive total cost analysis might provide additional information. Direct costs would increase if the equipment costs, such as the price of special electrodes, opioids, or infusion pumps were considered.

CONCLUSION

We conclude that, low-flow anesthesia technique demands expertise and attention from the anesthetist as risk of hypoxia and volatile anesthetic consumption do not differ regardless of the use of N_2O; Hence monitoring FiO_2 is essential. Both are safe to administer unless FiO_2 is lower than 30%. Future randomized controlled studies with larger sample sizes are needed to encourage N_2O free low-flow anesthesia. With appropriate remifentanil doses, air/O_2 provide better hemodynamic stability without increasing sevoflurane consumption. BIS-guided sevoflurane with its low solubility feature is better in quickly adapting the desired anesthetic depth levels.

Conflict of Interest: The authors declare that they have no conflict of interest.

Authors' contribution: Both authors took part in the concept, conduct of study, preparation of the manuscript and data analysis.

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I was on duty in a hospital in Azad Jammu & Kashmir, when in the evening hours our gynecologist called for a young unfortunate patient with twins and intrauterine death (IUD). She had had an episode of fits at home and the gynecologist planned to do hysterotomy. Inj magnesium sulphate infusion had been started at a rate of 1 gram/hr. On pre-anesthesia assessment, she was conscious and oriented, but her tongue was bitten and was swollen so much that she was unable to close her mouth completely. She was obese and her airway management was obviously difficult; compounded by a swollen tongue. Her platelet count was also low, so LSCS was planned under spinal anesthesia after arranging platelets. She was shifted to operating room and platelets were on the way. Monitoring was attached and we waited for platelets when suddenly patient started to become drowsy, her saturation began to fall, heart rate dropped from 110 to 65/min and her blood pressure also dropped. I put on the face mask to oxygenate her and was wondering what happened; then I realized that her infusion containing 25 gm of magnesium sulphate was completely empty. It had been infused in running. Suddenly patient stopped responding and her breathing effort vanished. It was very difficult to ventilate her with face mask. LMA or i-gel were not at hand. Her saturation failed to rise above 80%. I was puzzled what to do now, as I was alone with only an operating room assistant with me. Someone must have seen drops of sweat on my forehead as I could feel it flowing down my cheeks. I sent a call for the senior anesthesiologist and put laryngoscope in her mouth while praying to Allah. Unexpectedly her trachea was in front of me and it was not at all difficult as it seemed on previous assessment. I put ETT in and started ventilating the patient. Each breath I was giving to patient, I could feel my own saturation improving. Fortunately her heart rate and blood pressure did not fall further and responded to ionotropic support and IV fluids; her urine output was adequate. Platelets were transfused and surgical procedure ended smoothly. She was kept on ventilatory support overnight. Next day she was extubated and was alright. I was so relieved to see her awake and talking and thanked to Allah for helping me out. Vigilance is very truly the price of safety. Perhaps, controlled infusion of magnesium sulphate with syringe pump or infusion pump could have prevented this episode. Further, we need to have fully equipped difficult airway trolleys in every operating room complex.