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Original Article

Anaesthesia Section

Changes in Gas Composition during Low Flow Anaesthesia without Nitrous Oxide

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ABSTRACT

Introduction: Low flow anaesthesia utilising Oxygen (O_2) and Nitrous Oxide (N_2O) mixture carries a risk of hypoxia, but avoiding N_2O results in increased analgesic and volatile anaesthetic agent requirement.

Aim: This study attempted to find the lowest Fraction of inspired Oxygen (FiO_2) levels achieved with a mixture of 300 mL/min each of O_2 and medical air over two hours and to compare the overall analgesic requirement and cost while using similar flows of N_2O and O_2, respectively.

Materials and Methods: A prospective observational study was conducted between March 2015 and June 2016 at the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India. Patients of American Society of Anaesthesiologists (ASA) Grade 1 and 2 undergoing surgery under general anaesthesia with an endotracheal tube were included in the study, in two groups of 40 each. In the initial ten minutes following induction of anaesthesia, both groups received high Fresh Gas Flows (FGF) of 3 L/min each (Group O: medical air and oxygen; Group N: N_2O and oxygen), following which the FGF rates were reduced to 300 ml/min each. Any value of FiO_2 lesser than 0.3 during the duration of anaesthesia was considered to render the technique unsafe for clinical use. SPSS software version 20.0 was used to generate data and figures.

Results: The lowest FiO_2 recorded was 0.33 in Group O and 0.3 in Group N which occurred at the end of two hours. Mean analgesic requirement was significantly higher in Group O compared to Group N (151.85 µg, 124.85 µg; p-value=0.004) with a 62% increase in the cost incurred.

Conclusion: The use of medical air and oxygen in flows of 300 ml/min each following initial high flows of 3 L/min appears to be a safe technique. However, this combination was associated with an increase in the cost of anaesthesia and in the need for additional intra-operative analgesia.

Keywords: Anaesthetic agent, Environment, Fresh gas flow

INTRODUCTION

General anaesthesia with FGF at rates less than 2 L/min is associated with several advantages including improved pulmonary environment, mucociliary clearance and body temperature maintenance. In addition, it results in anaesthesia cost reduction of almost 75% [1-3] and has significant environmental benefits in terms of reduction in theatre pollution with anaesthetic gases [4].

The addition of N_2O, while aimed at reducing the harmful effects of high FiO_2, is also popular owing to its contribution to a stable level of anaesthesia, good analgesic properties and reduced perioperative opioid requirement [5,6]. However, there are several harmful effects of N_2O as well. First, owing to the risk of delivering a hypoxic mixture when using N_2O as a component of FGF, close patient monitoring is mandatory [7]. This may be a principal reason preventing a widespread adoption of low flow techniques by anaesthetists worldwide. The concentration of N_2O can increase under low FGF conditions owing to its reduced uptake with time as opposed to the consumption of oxygen at a constant rate. This may result in the build-up of N_2O in the circuit to dangerous levels with the patient at risk of receiving a hypoxic mixture. Constant gas monitoring is the only way to avoid such a complication. Second, N_2O causes expansion of gas filled cavities and increases the incidence of postoperative nausea and vomiting [8]. The other concerns with the use of N_2O include increased incidence of intra-operative awareness, myocardial infarction, impaired metabolism of vitamin B12 and folate, central nervous system disorders like myelopathies and Sub Acute Combined Degeneration (SACD) and a relative contraindication for neurosurgical procedures [9-11]. Finally, N_2O is a greenhouse gas that causes potential harm to the environment and health care personnel [7]. There is now a point of view that the use of nitrous oxide should cease completely in regular clinical practice.

In this study, we attempted to study the intra-operative gas changes with the use of N_2O-free anaesthesia with medical air and oxygen at low FGF rates of 300 mL/min each in a two-hour period. Our primary objective was to record the changes in anaesthetic agent and oxygen concentration and the least FiO_2 levels achieved, with the proposition that any value of FiO_2 below 0.3 would render this technique unsafe for clinical use. The analgesic requirements and cost difference and complication rates compared to low flow anaesthesia by using N_2O and oxygen in similar flows were also analysed.

MATERIALS AND METHODS

This was a prospective observational study that was conducted between March 2015 and June 2016 at the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, after the approval of the Institutional Ethical Committee. All patients provided a written informed consent for their inclusion in the study. As this study was planned as a feasibility study, a sample size of 40 was planned in each group. All patients were blinded to the procedure. The first author analysed the data and was blinded to the anaesthetic technique.

Patient selection: Patients in the age group of 18 to 60 years, with American Society of Anaesthesiologist, Physical Status (ASA PS) of 1 or 2 undergoing surgical operations requiring general anaesthesia with controlled ventilation and lasting more than two hours, were included in the study. Patients with chronic respiratory diseases

and those undergoing cardiothoracic and neurological operations or surgical operations with significant haemodynamic changes, were excluded from the study. Patients receiving any other form of analgesia were also excluded from the study. Patients that satisfied the inclusion criteria were randomized into one of the two groups, Group O (without nitrous oxide) and Group N (with nitrous oxide).

Anaesthesia: All patients were premedicated with morphine 0.1mg/kg intramuscularly and diazepam 5 mg orally prior to surgery. Intravenous access was secured and monitors were connected. All patients were pre oxygenated for three minutes with 100% oxygen and induced with 4-5 mg/kg of thiopentone and 2 µg/kg of fentanyl. Intubation was facilitated with 0.1 mg/kg of vecuronium.

Study group: After intravenous induction, anaesthesia was maintained in patients in the study group (Group O) according to standard institute protocol with 3 L/minute each of medical air and oxygen for three minutes, along with sevoflurane to achieve a Minimum Alveolar Concentration (MAC) of 1-1.2. After three minutes, the trachea was intubated, during which time, the flows were stopped. After intubation, a leak free circle system was connected and the gases were continued at the same flow rates for a further seven minutes. The FGF was reduced to low flow with 300 mL/min each of medical air and O_2 and the dial setting of sevoflurane was maintained to achieve a Minimum Alveolar Concentration (MAC) between 1-1.2 for the remaining duration of the surgery.

Anaesthesia in patients of Group N was maintained with oxygen and N_2O at flow rates of 3 L/min each and sevoflurane by using the same technique as described above, after intravenous induction of anaesthesia. At the end of 10 minutes, the flow rates of both oxygen and N_2O were reduced to low flow with each at 300 mL/min. The dial setting of sevoflurane vaporiser was adjusted to maintain MAC between 1-1.2. The main purpose of this group was for comparing the cost and analgesic requirements. The dial setting in the sevoflurane vaporiser was increased in increments of 0.5 in the event of an increase in the heart rate and blood pressure of the patient by more than 20% of baseline. Sevoflurane was reduced similarly if the Heart Rate (HR) and Systolic Blood Pressure (SBP) decreased more than 20% of baseline. In the event of persistent elevation of blood pressure or heart rate, fentanyl was administered intravenously in boluses of 20 µg. This was also based on the decision of the attending anaesthesiologist.

All patients were ventilated to achieve an $ETCO_2$ of 32-35 mmHg. The anaesthesia machine used was capable of delivering low flows (Aestiva/5 7100, Software Revision 1.X, GE Healthcare, Madison, WI). Amsorb® (Calcium Hydroxide and calcium chloride) was used as the CO_2 absorbent.

Data collection: The data was collected by using a multi-parameter monitor with facility for gas monitoring (Datex-Ohmeda S/5TM Monitor, GE Healthcare). The accuracy of gas monitoring was 0.2 with a rise time of <400 msec. The parameters monitored were ECG, HR, SpO_2, SBP, DBP, Fraction of Inspired Oxygen (FiO_2), End Tidal Oxygen (ETO_2), Fraction of Inspired Nitrous Oxide (FiN_2O), End Tidal Nitrous Oxide (ETN_2O), Fraction of Inspired Sevoflurane (FiSevo), End Tidal Sevoflurane (ETSevo), Fraction of Inspired Carbon Dioxide ($FiCO_2$), End Tidal Carbon Dioxide ($ETCO_2$), Minimum Alveolar Concentration (MAC) of sevoflurane and the dial setting of vaporiser. Data was recorded at five minute intervals.

Rescue measure: A drop in FiO_2 below 0.3 was fixed as the trigger to provide increased flows to administer a higher FiO_2. In case of a circuit disconnection intra-operatively, flows would be shut off and restarted following reconnection at the same flow rates.

The complications assessed were postoperative nausea and vomiting, intra-operative awareness (assessed by using Brice questionnaire), delirium and postoperative myocardial infarction.

Outcome measures: The changes in the gas composition, specifically FiO_2, was analysed to identify the safety of using medical air and oxygen in low flows over a period of two hours. Even a single recording of FiO_2 less than 0.3 would deem the technique as unsafe for clinical practice. The mean maximum and minimum values of FiO_2, ETO_2, FiSevo, ETSevo, MAC and $ETCO_2$ were measured in both the groups. Additionally, FiN_2O and ETN_2O were measured in group N. SPSS software version 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used to generate data and figures.

STATISTICAL ANALYSIS

The cost of sevoflurane was computed, based on the consumption of total liquid sevoflurane as demonstrated by the dial setting and FGF. The average cost incurred was compared between both the groups. Fentanyl requirements between the two groups were compared by using unpaired t-test.

RESULTS

Of the 80 patients satisfying the inclusion criteria, 10 were excluded for intra-operative haemodynamic instability (three patients), circuit disconnections and leaks (four patients) and prolonged time taken to intubate (three patients). Eventually, 35 patients were included in each group for analysis.

The patient demographics in both the groups were comparable [Table/Fig-1]. The mean inspired oxygen concentration in the first hour in Group O and N were 54.4±18 v/v% and 43.1±6.2 v/v%, respectively [Table/Fig-2]. At the end of second hour mean FiO_2 was 50.2±16.8 v/v% in Group O and 37.5±7.4 v/v% in group N. The least recorded FiO_2 value was 33 v/v% in Group O and 30 v/v% in Group N [Table/Fig-3]. There was no value recorded below 0.3 in the 140 study hours recorded.

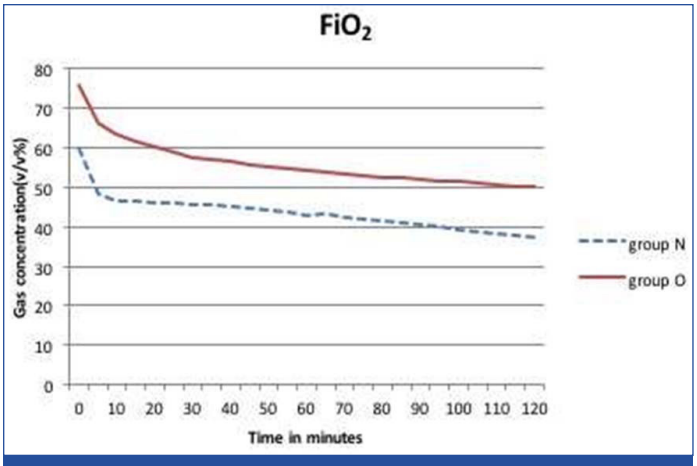
Comparison of the trends in mean inspired and end tidal oxygen concentration revealed ETO_2 to be greater than FiO_2 for the initial five minutes. Subsequently, it dropped to a level lower than FiO_2. The difference between FiO_2 and ETO_2 stabilized after a period of 20 minutes to a mean value of 2.8 v/v% (2.4-3 v.v%) for the remaining duration of observed anaesthesia.

In the control group, the uptake of N_2O declined following an initial period of higher uptake. After around 20 minutes on low flows, the N_2O concentration in inspired gas steadily increased as its uptake came down.

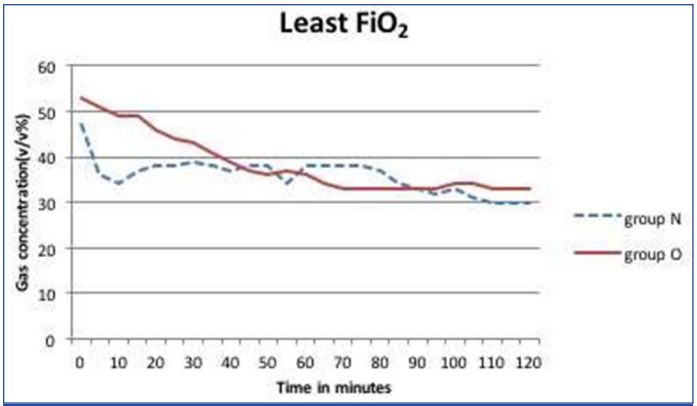
Dial settings for sevoflurane vaporiser in Group N was 4% during the initial 10 minutes in high flow and subsequently came down to 2%

Parameters	Group N	Group O	p-value*
Mean age (years)	45	45	0.9
Mean weight (Kg)	56.1	58	0.77
Male:female	4:3	5:2	0.31
ASA 1:ASA 2	22:13	16:19	0.62

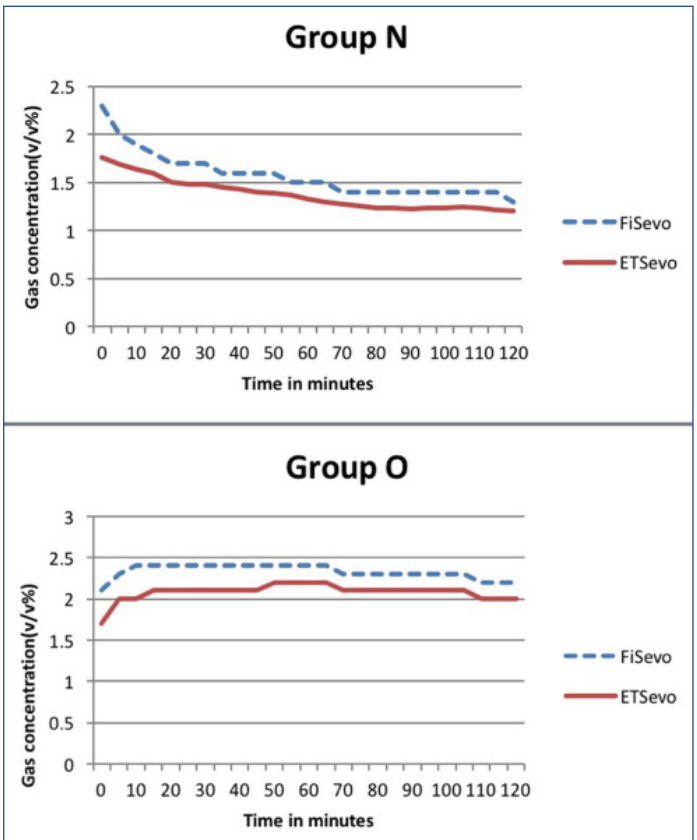
[Table/Fig-1]: Comparison of demographic data between the groups.
* Student's t-test



[Table/Fig-2]: Mean FiO_2 concentrations in Group O and Group N over two hours.



[Table/Fig-3]: Least FiO_2 levels attained in Group O and Group N over a two hour period.



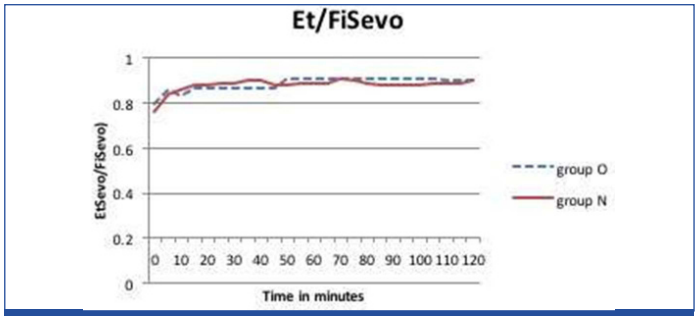
[Table/Fig-4]: Inspired and end tidal sevoflurane concentration in Group N and O.

in the first half hour, 3% during the following one hour and 2% till the end of two hours. In Group O, Dial setting was kept at 5% in high flows and subsequently reduced to 4% in first half hour in low flow, 5% in the subsequent hour and 4% till the end of two hours.

The inspired sevoflurane concentration was around 2±0.44 v/v% for the first 10 minutes in high flows. The concentration gradually reduced over the first hour to reach a level around 1.4±0.48 v/v% which was constant for the next one hour in Group N. In Group O, the mean inspired sevoflurane concentration in the initial few minutes was 2.1±0.60 v/v% which settled to a constant value of 2.3±0.60 v/v% for the rest of the period [Table/Fig-4].

In our study the difference between inspired and end tidal sevoflurane concentration was around 0.2-0.4 v/v% and 0.1-0.2 v/v% in the study and control groups, respectively. In the study group (Group O), the ratio of end tidal to inspired sevoflurane concentration reached a value of 0.8 in the first 15 minutes and as dial setting of sevoflurane was increased one hour after induction, the ratio became 0.9 within five minutes and remained constant after that. In Group N, the ratio of end tidal to inspired sevoflurane reached equilibrium of 0.9 in 15 minutes and remained constant throughout the study period [Table/Fig-5].

The MAC was maintained between 1-1.2 throughout the two hour



[Table/Fig-5]: Ratio of End tidal vs. Inspired concentration of sevoflurane in Group O and N over a two hour period.

Parameter	Group O	Group N
Mean Systolic Blood Pressure (mmHg)	107-120	107-120
Mean Diastolic Blood Pressure (mmHg)	55-70	62-76
Mean Heart Rate (beats/min)	72-94	73-92

[Table/Fig-6]: Haemodynamic variables in both the groups.

Agent	Flows	Group N		Group O	
		Volume (ml)	cost (INR)	Volume (ml)	Cost (INR)
Sevoflurane* (INR 19.4/ml)	High flows @ 6 L/min Low flow @600 ml/min	9.7 ml 9.2 ml	188 178.6	16.3 ml 16.3 ml	316.22 316.2
Nitrous oxide** (INR 190/1000 l)	High flow @3 L/min Low flow @ 300 ml/min for 110 min	30 000 ml 33 000 ml	5.7 6.27	-	
Oxygen** (INR 19/1000 l)	High flow @3 L/min Low flow @300 ml/min	30 000 ml 33 000 ml	0.57 0.63	30 000 ml 33 000 ml	0.57 0.63
Fentanyl (INR 36/100 µg)			INR 44.9		INR 54.6
Total cost***			INR 424.6		INR 688.2

[Table/Fig-7]: Comparison of the costs incurred between Group N and Group O in low flow anaesthesia.
*1ml of sevoflurane gives 184 ml of saturated vapour, according to the formula, Fluid (VA) mL = (specific wt) × Avagadro's constant × (273 + temp) ÷ (mol.wt × 273),
**The formula for the calculation of amount of volatile agent utilised is given by
Fluid vol.agent= (mean FGF × mean agent × duration) ÷ (sat.gas vol × 100)
***The cost of amsorb is not included in the analysis as there is no difference in the fresh gas flows.

period in both the groups. The end tidal carbon dioxide concentration was maintained between 33-34 mmHg in both the groups.

In the study group, the mean heart rate was 72-94 beats/min. The mean systolic and diastolic blood pressure was in the range of 107-120 mmHg and 55-70 mmHg, respectively. There were no significant fluctuations. Similarly, in the control group, the mean heart rate, systolic and diastolic blood pressure was 73-92/min, 107-120 mmHg and 62-76 mmHg, respectively [Table/Fig-6].

The mean total fentanyl requirements in the study (Group O) and control groups (Group N) were 151.85 µg and 124.85 µg, respectively. This difference between the two groups was statistically significant (p-value=0.0004).

None of the patients, followed up in this study, reported any awareness during surgery or postoperative nausea and vomiting. There were no incidences of delirium or postoperative myocardial infarction observed.

The total cost incurred for anaesthesia per patient in the study and the control groups was INR 688.2 and 424.6, respectively [Table/Fig-7] with a 62% increase in sevoflurane utilization in Group O.

DISCUSSION

The safety of using low flow anaesthesia is well established and its benefits in terms of cost savings, operation room and personnel

safety due to reduced wastage of anaesthetic gases, are universally accepted [1,2,12-15]. However, the use of nitrous oxide is being increasingly questioned in current practice. We performed this study to assess the safety of using oxygen in combination with medical air. We monitored intra-operative gas composition while using sevoflurane as the anaesthetic agent.

In this study, we set a fixed flow rate of 600 mL/min of FGF with the study group receiving 300 mL/min of O_2 and medical air and the control group receiving 300 mL/min of N_2O and O_2 each following an initial 10-minute period of high flows (three minutes before and seven minutes following intubation). The haemodynamic parameters, blood pressure and heart rate were stable throughout in both the groups on low flows without any fluctuations.

In a similar study using different proportions of N_2O and O_2, Virtue RW et al., monitored gas composition and reported that in the initial hour on low flows, the FiO_2 never dropped to less than 30%. In the group receiving N_2O and O_2 in a 50:50 ratio, Virtue RW et al recorded a FiO_2 of 24% as the least recorded value at the end of two hours [16]. In our study too, there were no recordings of FIO_2less than 30% and the least recorded value was 33 v/v%. During the initial five minutes in the control group, ETO_2 is higher than FiO_2 as there is rapid uptake of N_2O. The initial increase in ETO_2 more than that of inspired O_2 is attributable to the high initial alveolar uptake of nitrous oxide. Over time, as the nitrous oxide uptake decreases exponentially, the difference between the inspired and expired oxygen concentration stabilizes as the uptake of oxygen became constant.

Lin CY et al., found that the oxygen consumption is constant during general anaesthesia at the rate of 250-300 mL/min [17]. Although we did not directly measure O_2 consumption, we calculated the difference between the inspired and expired concentration of oxygen and found that after an initial period where the difference was high, indicating a higher uptake, it stabilized at 2.4-3 v/v% indicating a constant uptake of oxygen in both the groups. Bengston JP et al. and Raymond JA et al., have also reported similar observations. They have additionally found that the difference between FiO_2 and ETO_2 increases as the fresh gas flow decreases, a trend that is corroborated by our data [18,19].

The volume of gas in the circuit must be maintained to prevent the delivery of a hypoxic mixture. We have maintained a FGF of 600 mL/min in our study and a ratio of 50% oxygen was maintained in the study group. This is recommended for attaining FiO_2 of 0.3 in low flow anaesthesia as flow reduction may result in increased rebreathing of oxygen-depleted gas. In the control group, we observed a decline in the uptake of N_2O following an initial period of higher uptake. After around 20 minutes on low flows, the N_2O concentration in inspired gas steadily increased as its uptake came down. However, the minute-by-minute O_2 consumption remained constant. This highlights the potential for dangerous accumulation of N_2O in the circuit as oxygen concentration falls during prolonged anaesthesia in low flows. Such a risk is non-existent in the study group that received the oxygen-medical air mixture.

Sevoflurane is one of the newer inhalational agents that were initially discouraged from use in low flows for more than two MAC hours due to the risk of compound A formation. Sevoflurane degrades to compound A, which is found to be nephrotoxic in rats and the formation of compound A is more likely in low flow conditions. Therefore, it is now used frequently in low flows with alkali free CO_2 absorbents like Amsorb [20]. The rapid uptake and elimination of sevoflurane also favours its use in low flows. In this study we maintained a MAC between 1 to 1.2 and adjusted dial settings accordingly to achieve the same. The haemodynamic parameters also guided the titration of dial settings. The depth of anaesthesia was found to be adequate in all the patients in our study.

Several theories have been proposed to explain the uptake and distribution of gases during low and minimal flow anaesthesia. Two of the generally accepted ones are the Lowe's theory (that states that uptake is inversely proportional to square root of time) and the Lin's theory (that states that there is an initial wash-in period which equilibrates the entire circuit and the Functional Residual Capacity (FRC) of the patient with the anaesthetic gases following which there is only a constant uptake of gases throughout the duration of anaesthesia) [17]. Several studies have confirmed that the uptake of anaesthetic agents remains constant following an initial period of high uptake [12,21]. We were guided by Lin's theory and included an initial 10 minutes of high flows followed by a reduction in gas flow rates for the rest of the anaesthesia. This reduces the need for frequent changes in dial settings of the vaporiser and avoids complex calculations. Gorsky BH et al., pointed out that there is only a slight change in the uptake of anaesthetic agent during general anaesthesia [12]. In our study the difference between inspired and end tidal sevoflurane concentration was around 0.2-0.4 v/v% and 0.1-0.2 v/v% in the study and control groups, respectively. The ratio of expired to inspired concentration of sevoflurane reached a constant of 0.8 and 0.9 in the study and control groups, respectively, at 15 minutes. We also observed that an increase in dial setting after the first 30 minutes resulted in achieving a new equilibrium of 0.9 within five minutes. This is supportive of the assumption that the uptake of anaesthetic agent is constant after the gas concentration in the entire system reaches equilibrium.

Low flows also prevent wastage of gases, which is beneficial when using agents, like sevoflurane, which have a low uptake and require to be administered in high amounts to achieve a high partial pressure in the system and provide adequate depth of anaesthesia [1].

There is no generally accepted vaporiser dial setting in low flow anaesthesia and the only existing theoretical model has not been experimentally validated [21]. In our study, we attempted to standardise the vaporiser dial setting of sevoflurane while using low flows with air and oxygen mixture in order to avoid complex calculations. The dial settings were altered in increments or decrements of 0.5 whenever the heart rate or systolic blood pressure increased or decreased by 20%, as well as to maintain a MAC of 1 to 1.2.

Nitrous oxide is an integral part of general anaesthesia as it provides intra-operative analgesia and anaesthesia. But there is a theoretical risk of delivering a hypoxic mixture when using N_2O at low flow rates. Although many safety systems and monitors like oxygen ratio controller and link 25 have been developed and incorporated in newer anaesthesia machines and workstations to prevent the delivery of such a hypoxic mixture, these machines and monitors are not entirely fool proof. Of late, there is a growing concern that the use of N_2O might not be safe for the patient, the operating room personnel and the environment, in general. The usage of nitrous oxide has also been associated with expansion of gas filled cavities and postoperative nausea and vomiting and there are several studies linking the usage of nitrous oxide to peri-operative myocardial infarction [22,23].

Owing to these concerns nitrous oxide has been omitted during the administration of anaesthesia in many centres. However, owing to its analgesic and anaesthetic properties, its omission is expected to result in increased analgesic requirements intra-operatively [24]. Nitrous oxide also potentiates rapid induction and elimination of volatile anaesthetic agents, leading to lesser use of volatile anaesthetic agents, thereby reducing the cost of anaesthesia. Our data demonstrated a significant increase in fentanyl requirements in the study group compared to the control group.

Our cost calculations demonstrated a 62% cost increase when nitrous oxide was omitted. This increase in cost is attributed to the increased requirements of sevoflurane when using low flows without nitrous oxide with respect to the increased dial setting required to maintain a MAC of 1-1.2. But this factor can be offset by the fact that an anaesthetic practice that involves nitrous oxide will have

to be accompanied by inbuilt safety features and mechanisms to prevent the administration of a hypoxic mixture. The set-up of an effective safety system will result in significant increase in capital expenditure.

LIMITATION

Our study has several limitations. First, this study was designed as a preliminary study to establish the safety of low flow anaesthesia in the absence of nitrous oxide. The sample size of this study has not been assessed to demonstrate superiority or inferiority of one method over the other. Second, the sevoflurane dial setting arrived at in this study is yet to be validated. A prospective randomised controlled trial with adequate sample size may overcome these limitations.

CONCLUSION

Our study demonstrated that the use of medical air and oxygen in flows of 300 mL each following initial high flow rates of 3 L each for 10 minutes, for a period of two hours is a safe technique of low flow anaesthesia. Although, this technique resulted in greater analgesic requirement and overall cost per anaesthetic, it obviates the need for expensive monitoring systems required with the use of nitrous oxide mixture in low flow anaesthesia.

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