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RESEARCH ARTICLE

THE EFFECT OF NITROUS OXIDE ELIMINATION ON THE RATE OF DECLINE OF EXHALED CONCENTRATION OF ISOFLURANE DURING RECOVERY FROM GENERAL ANAESTHESIA; A COMPARATIVE STUDY TO INVESTIGATE THE PRESENCE OF REVERSE SECOND GAS EFFECT

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ABSTRACT:

Background: The second gas effect can also occur during emergence, with the rapid removal of nitrous oxide increasing the removal of other volatile anesthetics, a phenomenon known as the "reverse second gas effect". The aim of this study was to investigate the presence of this phenomenon. To achieve this study described the rate of decline of exhaled concentrations of isoflurane with and without nitrous oxide.**Methods*:*** One hundred patients undergoing surgery under general anesthesia with endotracheal intubation were randomly divided into two groups of fifty each. For Group I, when the gas analyzer monitor indicated an exhaled concentration of 1.2% isoflurane, with nitrous oxide at 66% and oxygen at 33% , the isoflurane was discontinued. For Group NI, when the gas analyzer indicated 1.2% exhaled concentration of isoflurane, with nitrous oxide at 66% and oxygen at 33%, the isoflurane and nitrous oxide both were discontinued, simultaneously. At the same time, the of flow for oxygen was increased to compensate for the loss of nitrous oxide flow. The duration for endtidal concentration of isoflurane to reduce from 1.2% to 0.4% is noted and compared between two groups.***Results:*** Significant difference in measured duration for decline of defined concentration of isoflurane with (36.72sec) and without nitrous oxide (54.04 sec) is noted ($p < 0.01$). ***Conclusions:*** Elimination of nitrous oxide during the recovery enhances elimination of isoflurane. This confirms the presence of reverse second gas effect.

INTRODUCTION: Inhaled anesthetic agents are the most commonly used drugs for the maintenance of general anesthesia. These agents may be used individually or in combination to produce desired level of anesthesia. When nitrous oxide is used in combination with other potent anesthetic agents like isoflurane during induction, it increases the rate of uptake of these potent inhaled anesthetics.[1,2,3] This phenomenon is known as the second gas effect.

Nitrous oxide may also be an adjunct to the elimination of anesthetic agents from the body. It may be theorized that any factor that increases uptake during induction also will have the same influence during emergence in the opposite way.[4] Since nitrous oxide speeds the rate of uptake of inhalational gases it should also speed the rate of elimination.[4]

This phenomena is known as the "reverse second gas effect". Minimal research has been done on the rate of decline (duration) of an exhaled anesthetic gas.[4,5] The rate of decline is measured as percent of exhaled gas. The actual existence of the reverse second gas effect is still a question.

Nitrous oxide has low blood gas partition coefficient which is 0.47. This allows rapid onset and high MAC

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of 105 which allows administration of nitrous oxide at higher concentration compared to potent inhaled anesthetic agents. Isoflurane has highest blood gas partition coefficient (1.45) among currently used agents in comparison with sevoflurane (0.69) and desflurane (0.42).

Since it is the solubility of nitrous oxide that allows either phenomenon to exist, research should examine if the "reverse second gas effect" exists with the more soluble anesthetic gas like isoflurane.[6] By studying the difference in time to exhale a set concentration of isoflurane with and without the use of nitrous oxide, the existence of this phenomena may be determined.[6,7]

The anesthesia provider may select from any number of anesthetic gases for surgical patient management. The choice is based on the patient's physical state, length of surgery, and cost of the gas.[8,9] A method that allows the patient to awaken from general anesthesia more quickly is seen as cost-efficient because it utilizes less surgical time and anesthesia interventions.[10,11]

This study was undertaken to provide data supporting the existence of a reverse second gas effect by using two low cost inhaled gases that may facilitate rapid awakening from anesthesia.

Aim and objective: The aim of this study was to investigate the presence of a "reverse second gas effect". To achieve this purpose the study described the rate of decline of exhaled concentrations of isoflurane with and without nitrous oxide.

The objective of the study was to find out whether discontinuation of nitrous oxide along with isoflurane, enhances the elimination of isoflurane and hence, in turn recovery from anesthesia.

MATERIALS AND METHODS: After the approval of our institution's ethics committee, study was conducted between September 2009 and May 2011. 100 subjects undergoing elective general anesthesia were selected for the study. Patients were selected on the day of their surgery after medical record review for inclusion and exclusion criteria.

Inclusion criteria:

a) Patients undergoing elective general anesthesia via endotracheal intubation.
b) Maintenance of anesthesia with isoflurane, nitrous oxide & oxygen.
c) Age above 18 years and below 65 years.
d) ASA physical status I and II.

Exclusion criteria:

a) Patients with cardiac or respiratory disorders.
b) Emergency surgeries.
c) Hemodynamic instability during preoperative or intraoperative period.
d) Pregnancy.
e) Presence of any gas filled or space occupying lesion.
f) Morbid Obesity.

After obtaining informed and written consent patients participating in the study were prepared for surgery in the same manner that all patients would be prepared. Patient charts were flagged to alert the assigned anesthesia providers that the patient is part of a study. The researcher did not provide or plan the anesthetic care for any of the participating patients.

The anesthesiologist who was not involved with this study induced anesthesia for all participants with standard intravenous induction medications. Anesthesia was delivered with circle system. Patients were maintained on volume controlled mechanical ventilation with appropriate tidal volume according to body weight. Induction and emergence was managed based on accepted standards of anesthesia care for the particular surgical procedure and patient needs.

Thirty minutes before the end of the surgery, based on an estimated surgical time, study was initiated. Subjects were divided into two groups for comparison purposes. In order to accomplish this, one card was removed from a envelope, which contained 100 cards. Fifty cards were labeled as "group I" and another fifty cards as "group NI". After removal, the card was not returned to the envelope. Appropriate data was recorded on the data collection sheet.

For Group I, when the gas analyzer monitor indicated an exhaled concentration of 1.0% isoflurane, with nitrous oxide at 70% (2 liters flow) and oxygen at 30% (1 liter flow). Next, the isoflurane was discontinued until the exhaled concentration reached 0.7%. This rate of decline, measured in seconds was recorded on the data collection sheet.

For Group NI, when the gas analyzer indicated 1% exhaled concentration of isoflurane, with nitrous oxide at 70% (2 liters flow) and oxygen at 30% (1 liter flow). Next, both isoflurane and nitrous oxide was discontinued, simultaneously. At the same time, the flow for oxygen was changed from 1 liter to 3 liters to compensate for the loss of liters of nitrous oxide flow. The rate of decline, measured in seconds was recorded on the data collection sheet.

Same stopwatch was used for all subjects. Constant alveolar ventilation is indicated by maintaining the end-tidal carbon dioxide ($ETCO_2$) at 35mmHg for all patients. Ventilator settings were kept constant throughout the time taken for rate of decline of set concentration of inhaled anesthetics. The study ended at the time when the gas analyzer indicated 0.7% isoflurane.

The patients continued to emerge from anesthesia and were extubated according to standards of care for all patients. The study in no way hindered the patients from receiving adequate and safe anesthesia. Both techniques used are currently used for general anesthesia and are accepted by the ASA.

The participants in the study received the same standards of care for all patients at the research site. No aspect of anesthetic care was withheld for the participants. All information obtained from the patient and their chart was kept confidential.

Data Analysis: Data analysis was done by using Students unpaired 't' test and Chi-square test. A statistical package SPSS version 11.5 was used for the analysis. P value < 0.05 was considered as significant.

OBSERVATIONS AND RESULTS:

Demographic Data: Demographic data assessed by student t test and two groups were found comparable with respect to age, sex, and weight distribution are with p value > 0.05 which is not significant.

Table 1 Group Statistics – Age, Weight

	GROUP	N	Mean	Std. Deviation	T
AGE	Group I	50	40.38	13.47241	0.31200
	Group NI	50	41.18	12.10446	p=0.755 ns
WT	Group I	50	58.78	9.23014	1.65700
	Group NI	50	61.76	8.74248	p=0.101 ns

Table 2 Group statistics (Sex)

			GROUP		Total
			Group I	Group NI	
SEX	Male	Count	25	26	51
		%	50.0%	52.0%	51.0%
	Female	Count	25	24	49
		%	50.0%	48.0%	49.0%
	Total	Count	50	50	100
		%	100.0%	100.0%	100.0%

Table 3 Group Statistics - ASA Physical Status

ASA Status		GROUP		Total
		Group I	Group NI	
I	Count	36	38	74
	%	72.0%	76.0%	74.0%
II	Count	14	12	26
	%	28.0%	24.0%	26.0%
Total	Count	50	50	100
	%	100.0%	100.0%	100.0%

x2=0.208 p=0.648 not significant

Comparison of End-tidal Concentration of Nitrous oxide: There was no significant difference in end tidal concentration of nitrous oxide at the start of the study (p > 0.05) between two groups. But the at the end of the study there was very highly significant difference (p<0.001) in end tidal concentration of nitrous oxide. This indicates significant washout of nitrous oxide in Group NI as required for the study.

Table 4 End-tidal Concentration of Nitrous Oxide

	GROUP	N	Mean Concentration (%)	Std. Deviation	T
End- tidal Concentration of Nitrous Oxide at Start	Group I	50	64.20	3.35030	1.74000
	Group NI	50	65.28	2.83592	p=0.085 ns
End-tidal Concentration of Nitrous Oxide at End	Group I	50	64.12	3.15995	31.80400
	Group NI	50	25.96	7.87390	P <0.001 vhs

Comparison of End-tidal Concentration of Carbon Dioxide: End-tidal concentration of carbon dioxide was comparable between two groups both at the start as well as at the end of the study. This indicates that constant alveolar ventilation was maintained during the study.

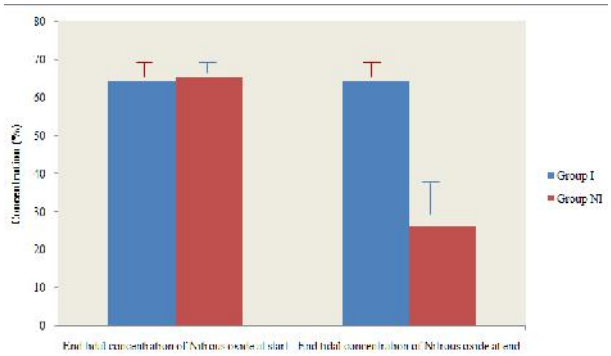

Figure 1 End-tidal concentration of nitrous oxide

Table 5 End-tidal Concentration of Carbon Dioxide

	GROUP	N	Mean Concentration (mmHg)	Std. Deviation	T
End-tidal Concentration of Carbon Dioxide at Start	Group I	50	39.10	1.58162	0.93600
	Group NI	50	32.26	2.95414	p=0.352 ns
End-tidal Concentration of Carbon Dioxide at End	Group I	50	31.78	2.93668	0.88900
	Group NI	50	32.30	2.91548	p=0.376 ns

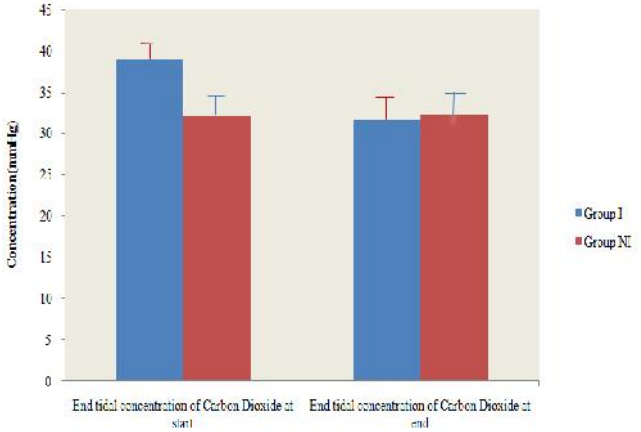

Figure 2 End-tidal Concentration of Carbon Dioxide

Comparison of Duration of Anesthesia: Mean duration of anesthesia was 153.3 minutes in group I and 123.8 minutes in group NI. There was no significant difference in duration of anesthesia between two groups as assessed by student t test ($p > 0.05$).

Table 6 Duration of Anesthesia

GROUP	N	Mean Duration (min)	Std. Deviation	T
Group I	50	153.30	87.72412	1.88300
Group NI	50	123.80	67.69198	p=0.063 ns

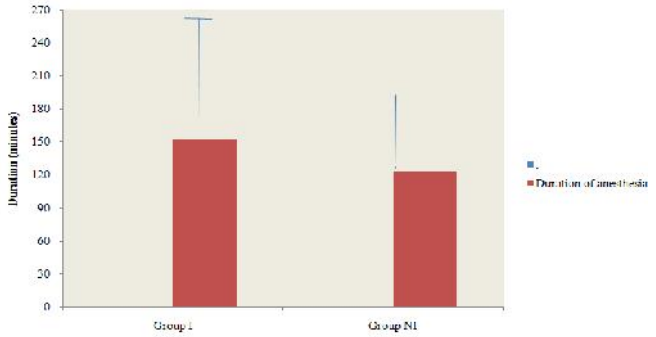

Figure 3 Duration of anesthesia

Comparison of Duration for Decline in Measured Concentration of Isoflurane: Analysis of duration for measured decline in isoflurane concentration by student t test has showed a very highly significant difference ($p < 0.001$) between two groups. This shows that elimination of nitrous oxide enhances the elimination of isoflurane during the recovery, indicating the presence of reverse second gas effect.

Table 7 Duration for Decline in Measured Concentration of Isoflurane

GROUP	N	Mean Duration (sec)	Std. Deviation	T
Group I	50	54.04	13.24180	7.43600
Group NI	50	36.72	9.79179	p<0.001 vhs

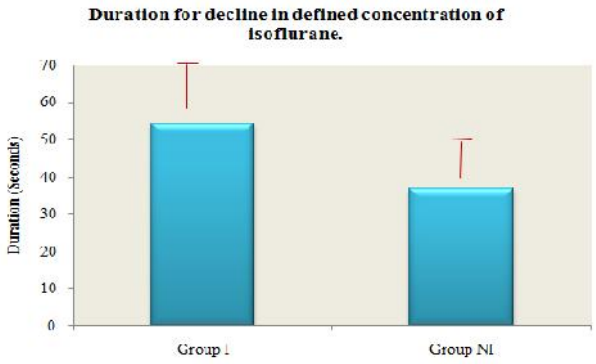

Figure 4 Duration for measured decline in isoflurane concentration

DISCUSSSION: The methods that hasten the recovery from inhaled anesthetic, especially agents with high solubility will allow early recovery. Isoflurane is the most soluble agent currently used in clinical practice. Speed of onset as well as recovery from isoflurane is slowest. It is usually used with nitrous oxide for the maintenance of anesthesia. Nitrous oxide has low solubility and is rapidly eliminated. Apart from this, it has MAC of 105 which allows it to use in high concentrations compared to potent inhaled anesthetics. This unique property of nitrous oxide causes second gas effect

during induction and enhances onset of anesthesia with potent inhaled anesthetic agents.

Diffusion hypoxia occurs during the recovery from nitrous oxide. This is due to rapid diffusion of nitrous oxide into the alveoli causing dilution of other gases in alveoli including oxygen, carbon dioxide and potent anesthetic agent. This creates a concentration gradient between blood and alveoli, and should enhance the elimination of potent anesthetic agent. Existence of this reverse second gas effect remains unproven as many of the previous studies gave contradictory findings.

This study was done to find out whether this property of nitrous oxide can be used during the recovery also. The study showed that duration required for elimination of isoflurane with nitrous oxide was significantly less (36.72 seconds) than that with isoflurane alone (54.04 seconds) with p value <0.001.

This study included only ASA I and II patients, without cardiopulmonary disease which can alter the pharmacokinetics of inhaled anesthetics. Patients with hemodynamic instability which can also alter the elimination of isoflurane and nitrous oxide were also excluded from the study.

Duration of anesthetic exposure was 153.3 seconds in group I and 123.8 seconds was in group NI. There was no significant difference ($p < 0.063$) between two groups. Maintenance of anesthesia for this duration allows equilibrium to occur at muscle group (approximately 2 hours) also in addition to vessel rich group.

The fresh gas flow rate of 3L was used during the study which is less than minute ventilation. This allowed rebreathing of exhaled isoflurane and nitrous oxide and the inspired concentration of these agents were not considered during the study period.

However study by Masuda T and Ikeda K[4] to investigate the presence of reverse second gas effect of nitrous oxide during recovery from halothane, also considered the inspired concentration during the study period and found that the elimination of nitrous oxide accelerates the elimination of halothane.

There was no significant difference in $ETCO_2$ at the start and at the end of the study between two groups. This indicates constant alveolar ventilation during the study period. Absence of fall in alveolar carbon dioxide with diffusion of nitrous oxide indicates that reverse second gas effect is may not be due to dilution of alveolar gases as shown in the study by Masuda T *et al.*[4]

CONCLUSION: This study concluded that,

1) The elimination of nitrous oxide enhances the elimination of isoflurane during the recovery.
2) The "reverse second gas effect" does exist during recovery when nitrous oxide is eliminated simultaneously with isoflurane.
3) This property of nitrous oxide can be used to accelerate the recovery from isoflurane.

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