

Effect of sevoflurane versus desflurane on blood glucose level in patients undergoing intracranial neurosurgery: A randomised controlled study

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ABSTRACT

Background and Aims: Anaesthetic agents can affect the neuroendocrine response to surgical stress. Along with affecting other parameters, this can affect blood glucose levels. This study aimed to compare the effect of sevoflurane and desflurane on hourly intraoperative blood glucose levels in non-diabetic patients undergoing intracranial surgery. **Methods:** A total of 70 adults (18–65 years) of American Society of Anesthesiologists physical status I and II undergoing elective intracranial surgery for supratentorial and infratentorial lesions were enrolled. Patients were randomised to receive either sevoflurane or desflurane as the maintenance anaesthetic agent. The blood glucose level was measured hourly after induction until the completion of surgery. Parametric tests, non-parametric tests, Friedman test, generalised estimating equations, Chi-square test, and Fisher's exact test were used to analyse the data. **Results:** In the sevoflurane group, the mean (standard deviation) blood glucose (mg/dL) increased from 93.34 (9.33) at the baseline to a maximum of 102.00 (8.61) at the 9 hours timepoint. This change was statistically significant ($P < 0.001$). In the desflurane group, the mean blood sugar (mg/dL) increased from 89.34 (9.85) at the baseline to a maximum of 92.37 (9.92) at the 4 hours timepoint and then decreased to 88.50 (0.71) at 9 hours timepoint. **Conclusion:** Desflurane caused an initial rise followed by a decline, whereas a gradual increase in intraoperative blood glucose level was seen with sevoflurane use in non-diabetic adult patients undergoing elective neurosurgery. The intraoperative change in blood sugar was statistically significant but was within the normal clinical range.

Key words: Blood glucose, desflurane, neurosurgery, sevoflurane

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INTRODUCTION

Surgical stress can cause hyperglycaemia due to neuroendocrine response, insulin resistance as well as increased secretion of counter-regulatory hormones. While hyperglycaemia is a known risk factor for neuronal damage, iatrogenic hypoglycaemia is equally detrimental to neural tissue. To decrease neuronal morbidity, perioperative sugars should be maintained in the normal range.^[1] Perioperative hyperglycaemia is associated with an increase in postoperative complications like surgical site and bloodstream infections, acute renal failure, prolonged ventilatory support, increased hospital costs, as well as higher mortality.^[2]

Surgical stress, intravenous fluids, and different anaesthetic agents affecting systemic and cerebral metabolism of glucose are the chief determinants of perioperative blood glucose levels. The metabolic alteration of surgical stress can be

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achieved with sufficient analgesia and depth of anaesthesia.^[3] Anaesthetic agents are known to affect the neuroendocrine surgical response and alter insulin release even without surgical stress, leading to changes in blood glucose levels.^[4-6] There is equivocal literature demonstrating the effect of various inhalational anaesthetic agents on perioperative glucose levels in neurosurgical patients.^[4-6] The effect of desflurane on glucose metabolism has not been seen *in vitro*; however, *in vivo* studies show increased intraoperative blood glucose levels with its use.^[6]

Sevoflurane and desflurane are two popular inhalational agents widely used in neuroanaesthesia due to their favourable effects on cerebral metabolism, preservation of carbon dioxide reactivity and rapid emergence. The two inhalational agents might have different effects on obtunding the stress response to surgery which can manifest as variation in blood glucose levels. This double-blind randomised controlled study aimed to compare the effect of sevoflurane and desflurane on blood glucose levels and determine the hourly trends of intraoperative blood glucose in adult, non-diabetic patients undergoing intracranial surgery. The objective of this study was to estimate the hourly blood sugar levels with the intraoperative use of sevoflurane and desflurane. The outcome parameter was the hourly change in intraoperative blood glucose levels with the use of sevoflurane or desflurane as a maintenance inhalational agent.

METHODS

This prospective randomised controlled study was conducted at the neurosciences centre of our institute from December 2017 to November 2018 after obtaining approval from the institutional ethics committee (AIIMS/IEC/393/04.08.2017, RP-11/2017). The trial was registered with the Clinical Trials Registry of India (CTRI/2017/12/010790). Written informed consent was taken from the patient and nearest kin after a thorough explanation of the purpose and procedure and the study was done under the principles of the declaration of Helsinki.

All consenting patients of either gender, aged between 18-65 years, belonging to the American Society of Anesthesiologists physical status I or II scheduled for supratentorial or infratentorial neurosurgery with either sevoflurane or desflurane as the maintenance agent were enrolled. Patients suffering from diabetes, disorders of glucose metabolism, thyroid dysfunction,

renal or hepatic disease, on steroids, beta-adrenergic blocking agents, insulin or oral hypoglycaemic agents, pregnant or lactating patients and chronic alcoholic patients were excluded from the study. The enrolled patients were randomised to either sevoflurane or desflurane group, based on a sequence of computer-generated random numbers.

The sealed opaque envelope method was used for allocation concealment. The treating anaesthesiologist opened the envelope and gave anaesthesia to the patient. The patient and the statistician who analysed the data were blind to the study groups.

According to our institutional preoperative fasting protocol, patients completed 8 hours of fasting for solid foods before the conduct of anaesthesia.^[7] Non-invasive blood pressure, pulse oximetry, electrocardiography, and temperature probe were attached to the patient after transfer to the operating room. After securing the intravenous cannula, the radial artery was cannulated under local anaesthesia. Baseline (T0) blood glucose was determined from arterial blood. Patients were pre-oxygenated with 100% oxygen at 6 litres/minute and anaesthesia induction was achieved with intravenous fentanyl (2 µg/kg), propofol (dose titrated for the loss of verbal response) and rocuronium 1 mg/kg. The airway was secured with a tracheal tube of appropriate size. According to randomisation, anaesthesia was maintained using either sevoflurane or desflurane in a mixture of 40% oxygen and 60% nitrous oxide to achieve a minimum alveolar concentration of 0.5 to 1. The anaesthetic depth was titrated to achieve a bispectral index score (BIS) between 40 and 60 at all-time points. Intravenous fentanyl (1 µg/kg/h) and rocuronium (0.3 mg/kg/h) were given as a continuous infusion. End-tidal carbon dioxide was maintained between 30 mmHg and 35 mmHg. The nasopharyngeal temperature was measured and the temperature was maintained between 36°C and 37.2°C. Non-glucose-containing fluid [normal saline (0.9%)] was used in the intraoperative period. Vital parameters [mean arterial blood pressure and heart rate] were continuously recorded and maintained around the baseline value $\pm 20\%$.

The glucose level was measured hourly, after induction until completion of the surgery, by collecting 1 ml blood in a 2 ml syringe from the arterial line using point of care, glucose oxidase peroxidase method (one-touch select simple blood glucose meter, Life scan, Europe, Switzerland).

The number-coded syringes were labelled and assessed in a double-blinded manner. Hypoglycaemia was defined as an intraoperative blood sugar level of less than 70 mg/dL and was planned to be treated with intravenous glucose. Hyperglycaemia was defined as a blood glucose level of more than 200 mg/dL and was planned to be treated with an appropriate dose of regular insulin infusion to maintain blood glucose levels within the range of 140–180 mg/dL. At the end of the procedure, neuromuscular blockade was reversed and the trachea was extubated when the patient was fully awake. Patients with poor recovery (patients who were not fit for extubation after surgery in the operating room) were shifted to the intensive care unit (ICU) for elective mechanical ventilation and close monitoring. Multimodal analgesia consisting of non-steroidal anti-inflammatory drugs and opioids was used to take care of postoperative pain. Hospital stay and ICU stay (in days) were noted.

The sample size for the study was based on a minimum clinically important difference of 5.00 and a standard deviation of 5.00 for change in blood glucose. The sample size required in each arm of the study was calculated with an effect size of 1.00, α of 0.05, β of 0.05 and power of 0.95. Based on the formula, the minimum calculated sample size for each arm was 27 (total = 54). Keeping an attrition of 20%, the final sample size was 35 per arm.

Statistical analysis was performed using Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, Illinois, United States of America). Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed in number and percentage. Parametric tests (t-tests) were used to make group comparisons for the duration of surgery. Non-parametric tests (Wilcoxon/Mann-Whitney U Test) were used to make group comparisons for age, weight, amount of intraoperative fluid, hospital and ICU stay and blood glucose (mg/dL) at each of the time points. Since data were non-normally distributed, the Friedman test was used to explore the change in blood glucose over time within each group. The generalised estimating equations method was used to explore the difference in change in blood glucose (mg/dL) between the two groups over time. The association between different categorical variables and groups was tested by the Chi-square test and Fisher's exact test, whichever was appropriate. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 70 patients were included in the study [Figure 1]. The distribution of diagnosis, demographic, baseline, and intraoperative variables was comparable between the groups [Table 1]. The blood loss, blood transfusion, and use of mannitol were comparable between the two groups [Table 1]. All patients had a preoperative Glasgow coma scale of 15. No patient had a midline shift in computed tomography of the brain or signs of raised intracranial pressure.

Baseline blood glucose values were comparable in both groups [Table 2]. In the sevoflurane group, the mean blood sugar (mg/dL) increased from 93.34 (9.33) at the baseline to a maximum of 102.00 (8.61) at the 9 hours timepoint. This change was statistically significant ($P < 0.001$). In the desflurane group, the mean blood glucose (mg/dL) increased from 89.34 (9.85) at the baseline to a maximum of 92.37 (9.92) at the 4 hours timepoint and then decreased to 88.50 (0.71) at the 9 hours timepoint. This change was not statistically significant ($P = 0.144$) [Table 2]. There was a significant difference in the trend of blood glucose (mg/dL) over time between the two groups ($P < 0.001$).

Vitals including heart rate and mean arterial pressure were comparable in both groups [Table 3]. There were no episodes of hypoglycaemia or hyperglycaemia in any of the groups. Duration of hospital and ICU stay was similar in both groups.

DISCUSSION

Hyperglycaemia can cause inflammation and impaired microcirculation leading to cerebral effects (ischaemia, oedema, intracranial hypertension) and systemic effects (osmotic diuresis, hypovolaemia, hypotension and immunodepression). Neurosurgeries especially around specific brain areas like the insular cortex or direct hypothalamic damage/irritation of glucose regulatory centres have been seen to be associated with alteration in glucose metabolism.^[8] Patients undergoing neurosurgical procedures are prone to neuronal injury associated with hyperglycaemia.^[1] Besides neuronal protection, there are many perioperative advantages of blood glucose control.^[8,9]

Though the mechanism remains unclear, volatile anaesthesia with isoflurane and sevoflurane has been found to impair glucose tolerance and insulin

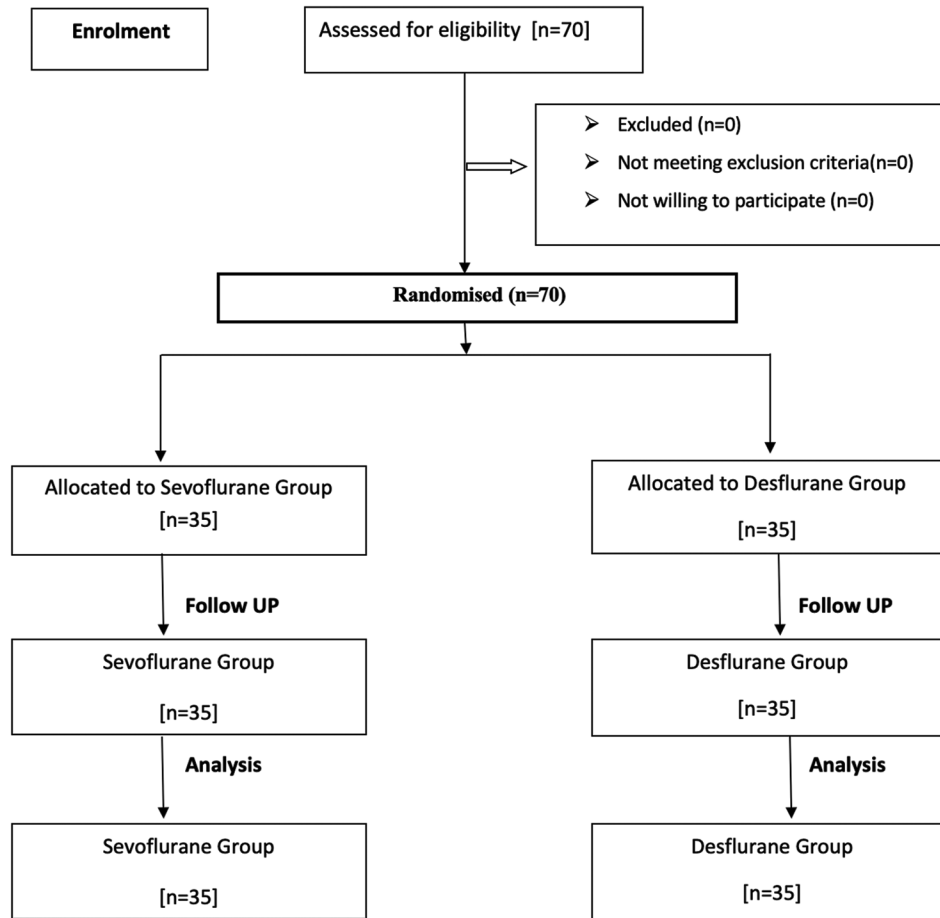


Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram

secretion in animal and human studies.^[4,5] Isoflurane is known to cause a decrease in insulin secretion due to K^{ATP} channel activation in pancreatic β cells predisposing patients to hyperglycaemia.^[4] Many animal studies and *in vitro* models demonstrate the variable effects of volatile anaesthetics on glucose metabolism. Stella P *et al.* demonstrated that both isoflurane and sevoflurane caused insulin resistance in a canine model.^[10] *In vitro* pharmacokinetic studies demonstrated that desflurane has no direct effect on the metabolism of glucose but the *in vivo* intraoperative blood glucose level may rise.^[6] Dikmen B *et al.*^[11] found that sevoflurane and desflurane administration in hyperglycaemic rats was associated with an insignificant increase in blood glucose levels in the early as well as late post-anaesthesia period.

Clinical studies have documented variable results. Tanaka *et al.*^[5] compared the dose-dependent effects of sevoflurane and isoflurane anaesthesia on glucose tolerance and concluded that both sevoflurane and isoflurane anaesthesia impair glucose tolerance to the

same extent. Another study documented that volatile anaesthetics do not prevent metabolic endocrine responses to surgery.^[12] The use of desflurane/remifentanyl and desflurane/epidural anaesthesia decreases the intraoperative rate of whole-body glucose production, thereby attenuating the hyperglycaemic response to colorectal surgery.^[13] In another study, desflurane was associated with better control of intraoperative cortisol and adreno-corticotrophic hormone response when compared to sevoflurane. However, both gases did not influence the plasma levels of interleukin-6, C-reactive protein, and glucose.^[14] Baldini G *et al.* reported an increasing trend of blood glucose irrespective of the depth of desflurane anaesthesia.^[15]

Limited studies are looking at intraoperative blood glucose levels with the use of sevoflurane and desflurane anaesthesia in patients undergoing elective neurosurgery. In a recently published study by Halder *et al.*,^[16] changes in blood glucose levels were seen with the use of volatile (sevoflurane and

Table 1: Demographic and other variables

Parameters	Sevoflurane (n=35)	Desflurane (n=35)	P
Age (years) Mean±SD	36.91±13.2	40.14±14.23	0.359 ¹
Gender [n (percentage)]			0.231 ²
Male	19 (54.3%)	14 (40.0%)	
Female	16 (45.7%)	21 (60.0%)	
Weight (kg) Mean±SD	60.46±12.69	60.71±11.25	0.715 ¹
Duration of surgery (Hours) Mean±SD	7.42±2.21	7.38±1.30	0.934 ¹
Comorbidities [n (percentage)]			0.177 ⁴
None	27 (77.1%)	27 (77.1%)	
HTN	5 (14.3%)	8 (22.9%)	
Hypothyroidism	3 (8.6%)	0 (0.0%)	
Intraoperative fluid [n (percentage)]			0.239 ⁴
NS	32 (91.4%)	35 (100.0%)	
NS + HES	3 (8.6%)	0 (0.0%)	
Amount of Intraoperative Fluid (L) Mean±SD	3.87±1.55	3.81±0.76	0.595 ¹
Duration of Anaesthesia (Hours) Mean±SD	8.17±2.41	8.13±1.31	0.929 ¹
Hypoglycaemic/Hyperglycaemic Episode (Yes)	0 (0.0%)	0 (0.0%)	1.000 ²
Hospital Stay (Days) Mean±SD	9.51±2.97	9.06±3.42	0.661 ¹
ICU Stay (Days) Mean±SD	6.20±2.03	6.57±3.16	0.762 ¹
Haematocrit (%) Mean±SD	36.40±3.52	36.03±3.75	0.671 ³
Blood Transfusion.			1.000 ⁴
Yes	3 (8.6%)	2 (5.7%)	
No	32 (91.4%)	33 (94.3%)	
Mannitol Use			0.229 ³
Yes	22 (62.8%)	25 (71.4%)	
No	13 (37.1%)	10 (28.6%)	
Blood Loss (mL)			0.304 ¹
Mean±SD	360.00 (74.56)	337.14 (77.0)	
Diagnosis [n (percentage)]			
supratentorial glioma	21 (60%)	25 (71.4%)	
Infratentorial cerebello-pontine angle lesion	11 (31.4%)	7 (20.0%)	
Moya Moya disease	3 (8.6%)	3 (8.6%)	

Significant at $P < 0.05$, 1: Wilcoxon/Mann-Whitney U Test, 2: Chi-squared Test, 3: *t*-test, 4: Fisher's exact test. SD – standard deviation, *n* – number, HTN – hypertension, NS – normal saline, HES – hydroxyethyl starch, ICU – intensive care unit

Table 2: Comparison of the two groups for blood glucose (mg/dL)

Time points of Blood Glucose (mg/dL) measurement.	Blood Glucose (mg/dL)		P value (between the groups) (Wilcoxon/Mann-Whitney U Test)
	Sevoflurane Mean (SD), <i>n</i>	Desflurane Mean (SD), <i>n</i>	
Baseline	93.34 (9.33), 35	89.34 (9.85), 35	0.121
Post-induction	98.31 (9.83), 35	89.37 (10.00), 35	0.001
1 hour	98.60 (9.43), 35	90.34 (9.57), 35	0.001
2 hours	97.82 (8.78), 34	91.29 (9.64), 35	0.006
3 hours	97.24 (8.40), 34	92.11 (9.47), 35	0.035
4 hours	98.06 (9.26), 33	92.37 (9.92), 35	0.025
5 hours	98.19 (9.01), 31	92.00 (9.97), 32	0.024
6 hours	98.90 (8.95), 29	91.04 (10.62), 28	0.010
7 hours	99.36 (9.36), 22	91.06 (11.47), 18	0.033
8 hours	99.62 (8.23), 16	91.50 (10.56), 8	0.086
9 hours	102.00 (8.61), 15	88.50 (0.71), 2	0.062
P value for change in blood glucose (mg/dL) over time within each group (Friedman test)	<0.001	0.144	
Overall P value for comparison of change in blood glucose (mg/dL) over time between the two groups (generalised estimating equations)	<0.001		

SD – standard deviation, *n* – number

desflurane) as well as intravenous (propofol) agents in patients undergoing supratentorial glioma surgery.

The authors found an increase in blood glucose levels with the increasing duration of anaesthesia.

Table 3: Comparison of the two groups for mean arterial pressure and heart rate over time

Time Point	Mean arterial pressure (mmHg)			Heart rate		
	Sevoflurane (n=35)	Desflurane (n=35)	P	Sevoflurane (n=35)	Desflurane (n=35)	P
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Baseline	86.83 (8.24)	87.66 (7.57)	0.615	77.66 (10.56)	76.94 (10.50)	0.777
1 hour	90.86 (8.26)	90.51 (8.90)	0.920	84.74 (11.89)	80.63 (11.14)	0.140
2 hours	89.03 (9.01)	88.51 (9.94)	1.000	80.80 (10.35)	80.46 (10.92)	0.893
3 hours	85.43 (8.64)	86.06 (9.58)	0.819	77.91 (12.35)	76.34 (13.16)	0.608
4 hours	85.68 (8.46)	85.00 (9.60)	0.678	78.06 (12.11)	75.51 (11.45)	0.373
5 hours	85.12 (8.80)	84.66 (9.53)	0.738	79.64 (12.63)	75.19 (8.87)	0.105
6 hours	84.24 (8.43)	83.81 (8.79)	0.893	79.36 (11.86)	79.00 (9.49)	0.895
7 hours	84.65 (6.24)	84.41 (8.64)	0.583	78.50 (11.79)	78.12 (8.52)	0.906
8 hours	82.70 (5.11)	81.88 (8.18)	0.919	77.21 (8.32)	77.50 (9.68)	0.942
9 hours	81.88 (6.17)	85.33 (6.43)	0.488	76.00 (13.39)	78.75 (10.69)	0.677

SD – standard deviation, n – number

We found an increasing trend of blood glucose levels in the sevoflurane group throughout the surgery. However, in the desflurane group, the blood sugar level increased till the fourth hour of surgery though later on, there was a decreasing trend till the end of surgery. These changes, when compared to the baseline levels, were found statistically significant in the sevoflurane group. In the sevoflurane group, statistically significant changes in the blood glucose level were seen in comparison to the desflurane group at different time points. This difference in findings from the study by Halder *et al.*^[16] may be because of different inclusion criteria. We included both supratentorial and infratentorial tumours, whereas Halder *et al.*^[16] included only supratentorial tumours. The changes in blood glucose in any of the groups did not reflect clinically and there were no episodes of hypoglycaemia or hyperglycaemia in either group.

The implications of the findings of this study may not be of significance for patients without co-morbidities; however, the findings may be of importance in those with diabetes and other disorders of glucose metabolism. Further studies looking at the effect of these agents in vulnerable patients may be clinically more meaningful, especially in neurosurgical procedures which are known to last for a prolonged duration.

Despite the limitations of being a single-centre, intraoperative study on non-diabetic patients, our study is an attempt at defining the pattern of intraoperative glucose levels in neurosurgical patients undergoing prolonged duration surgery under sevoflurane and desflurane anaesthesia. Our study could not demonstrate any clinically significant changes in the blood sugar levels with the use of either agent and could not demonstrate a definite relation between changes in glucose levels and anaesthetic drugs.

Nevertheless, we cannot deny the clinical relevance of our findings in vulnerable patients. A future study in diabetic, critically ill patients, along with stress markers like catecholamines and hormones, may be helpful to address this issue.

CONCLUSION

Our study demonstrates a pattern of change in blood glucose with intraoperative use of sevoflurane and desflurane in non-diabetic, ASA I and II patients undergoing neurosurgery. The intraoperative change in blood sugar was statistically significant but was within the normal clinical range. Studies looking at the magnitude of change in at-risk patients like diabetics, those on steroids and the critically ill should be undertaken to look into its clinical relevance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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