CEREBRAL LACTATE EFFLUX DURING GENERAL ANAESTHESIA- A COMPARISON BETWEEN MAINTENANCE OF ANAESTHESIA WITH SEVOFLURANE AND WITH PROPOFOL INFUSION

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ABSTRACT

BACKGROUND
Anaesthetic agents substantially reduce the global cerebral metabolic rate and blood flow. Glycolytic metabolism increases in response to ischaemic events.

The aim of the study is to know whether there is any difference in lactate production with inhalational agents compared with intravenous agents for maintenance of anaesthesia.

MATERIALS AND METHODS
This is an observational study conducted on 60 adult patients of ASA I and II undergoing ENT and neurosurgical procedures under general anaesthesia divided into two groups of 30 each with maintenance of anaesthesia with sevoflurane and with propofol infusion, in groups I and II, respectively. Blood samples were drawn from the internal jugular vein and subjected to blood gas analysis. Statistical analysis was done and p-value was calculated.

RESULTS
Intravenous agents are associated with a greater degree of anaerobic glucose metabolism and hence higher cerebral lactate levels. Thus, inhalational agents are beneficial in maintaining cerebral flow by reducing anaerobic metabolism of glucose.

CONCLUSION
Alterations in cerebral blood flow and ischaemia are lesser with inhalational agents compared to intravenous agents.

KEYWORDS
Cerebral Lactate, Intravenous Anaesthetic Agents, Inhalational Agents, Maintenance of Anaesthesia.

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BACKGROUND
General anaesthetics are a structurally diverse class of drugs that produce a common endpoint, a behavioural state referred to as general anaesthesia. In the broadest sense, general anaesthesia can be defined as a global, but reversible depression of central nervous system function resulting in the loss of response to and perception of all external stimuli.

It is important to remember that general anaesthesia is useful only in so far as it facilitates the performance of surgery or other noxious procedures. The performance of surgery usually requires an immobilised patient who does not have an excessive autonomic response to surgery (blood pressure and heart rate) and who has amnesia for the procedure. Thus, the essential components of the anaesthetic state are immobilisation, amnesia and attenuation of autonomic responses to noxious stimulation. Indeed, if an anaesthetic produces profound amnesia, it can be difficult in principle to determine if it also produces either analgesia or unconsciousness.

Anaesthetic agents substantially decrease the global cerebral metabolic rate and blood flow with a degree of regional heterogeneity characteristic to that agent. It is hypothesised that inhalational agents are beneficial in case of reduction of net cerebral lactate efflux as they cause cerebral vasodilatation and increased cerebral blood flow.1

Serum lactate is a biomarker, which estimates the probability and extent of tissue hypoperfusion.

Our study aims to know whether there is any difference in lactate production as a measure of the global cerebral metabolic rate and blood flow with inhalational agents compared to intravenous agents for maintenance of anaesthesia.

MATERIALS AND METHODS
This is an observational study conducted at Sree Gokulam Medical College and Research Foundation, Trivandrum. Patients in the age group of 20 to 60 years-

a. With ASA I/II,

b. Who were undergoing ENT and neurosurgical procedures,
c. Under general anaesthesia,

d. Who were willing to participate in the study were included.

A total sample size of 60 in 2 groups of 30 each. Duration of the study was 6 months from April 2016 to September 2016.

Ethical Consideration

Study will be conducted only after getting ethical clearance from the institutional ethical committee and after obtaining consent from the patient.

Procedure- After obtaining institutional ethical committee clearance and informed consent, the patient is kept nil by mouth for 8 hours. Both groups were premedicated with midazolam 0.02 mg/kg, glycopyrrolate 0.004 mg/kg and ondansetron 0.15 mg/kg. ECG, pulse oximetry, NIBP, ETCO₂, agent and MAC monitoring were conducted. Inj. Fentanyl 2 micrograms/kg IV was administered to all patients. All patients were pre-oxygenation with 6L of oxygen. Induction was done with propofol 1-2 microgram/kg IV. Muscle relaxant used for intubation was Inj. Atracurium 0.5 mg/kg.

**Maintenance in Group I**- Initial fresh gas flow rate 6 L/minute (3:3 - oxygen:air) and a dial setting on sevoflurane vaporiser to maintain intraoperative MAC of 1. Later fresh gas flow reduced to 2L (1:1 - oxygen:air) with circle system. Inj. Fentanyl 1-2 micrograms/kg/hour infusion was kept and then titrated to get favourable haemodynamics.

Mechanical ventilation was initiated with a tidal volume of 6-8 mL/kg.

- Respiratory rate was adjusted to keep ETCO₂ at 30-35.
- Maintained intraoperative MAC of 1.

**Maintenance in Group II**- Initial fresh gas flow rate 6 L/minute (3:3 - oxygen:air) and a dial setting on sevoflurane vaporiser to maintain intraoperative MAC of 1. Later fresh gas flow reduced to 2L (1:1 - oxygen:air) with circle system. Infusion of propofol at 25-80 micrograms/kg/hour with fentanyl at 1-2 micrograms/kg/hour titrated to maintain favourable haemodynamics. Respiratory rate was adjusted to keep ETCO₂ at 30-35.

**Comparison of the Two Study Groups**- Demographic characteristics - age, gender and weight were measured. Two samples were taken from the right internal jugular vein and sent for blood gas analysis. The first sample was taken 5 minutes after the induction of anaesthesia and the second one was taken just prior to extubation. Statistical Analysis - SPSS Version 20. P values - calculated using paired T-test.

**RESULTS**

We investigated the effect of anaesthetic agents on net cerebral lactate efflux by measuring internal jugular vein lactate values. No statistically significant difference with respect to the demographic parameters amongst the two groups. A total of 60 patients were included in the study. End-tidal carbon dioxide levels were comparable. Duration of the study was between 50-90 minutes in both groups. In our investigation, we studied CBF and metabolism aiming at PaCO₂ levels of 30 and 50 mmHg. We chose these PaCO₂ levels because they roughly reflect the range of unintended variations of PaCO₂ that often occur in routine clinical practice (Table 1).

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Due to the controlled adjustment of mechanical ventilation, the variability of PaCO₂ at both target levels was small. The body temperature of the patients was effectively kept constant. None of the patients showed increased levels of blood glucose. RBS values were comparable. There was no hypoglycaemia allowed (Table 1).

**Maintenance in Group II**- Initial fresh gas flow rate 6 L/minute (3:3 - oxygen:air) and a dial setting on sevoflurane vaporiser to maintain intraoperative MAC of 1. Later fresh gas flow reduced to 2L (1:1 - oxygen:air) with circle system. Infusion of propofol at 25-80 micrograms/kg/hour with fentanyl at 1-2 micrograms/kg/hour titrated to maintain favourable haemodynamics. Respiratory rate was adjusted to keep ETCO₂ at 30-35.

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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n=30)</th>
<th>Group II (n=30)</th>
<th>Range I</th>
<th>Range II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.83 ± 11.335</td>
<td>39.03 ± 11.025</td>
<td>20-57</td>
<td>20-57</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.97 ± 9.004</td>
<td>63.07 ± 9.017</td>
<td>46-78</td>
<td>46-78</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>32.17 ± 1.642</td>
<td>31.97 ± 1.47</td>
<td>30-35</td>
<td>30-35</td>
</tr>
<tr>
<td>Duration</td>
<td>66.50 ± 9.016</td>
<td>67.83 ± 9.621</td>
<td>50-90</td>
<td>50-90</td>
</tr>
<tr>
<td>GRBS</td>
<td>135.23 ± 18.778</td>
<td>135.33 ± 21.189</td>
<td>104-176</td>
<td>100-180</td>
</tr>
<tr>
<td>IJV lactate in sample 1</td>
<td>1.154 ± 0.32174</td>
<td>1.137 ± 0.31725</td>
<td>0.56-1.95</td>
<td>0.45-1.98</td>
</tr>
<tr>
<td>IJV lactate in sample 2</td>
<td>1.4747 ± 0.36794</td>
<td>2.3333 ± 0.6406</td>
<td>1.00-2.09</td>
<td>1.34-3.65</td>
</tr>
</tbody>
</table>

**Table 1. Demographic Data and Study Variables in Group I and II**

Due to the controlled adjustment of mechanical ventilation, the variability of PaCO₂ at both target levels was small. The body temperature of the patients was effectively kept constant. None of the patients showed increased levels of blood glucose. RBS values were comparable. There was no hypoglycaemia allowed (Table 1).

**Table 2. Mean Difference between IJV Lactate Levels in Group I and II**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean Standard Deviation</th>
<th>Standard Error of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>30</td>
<td>0.3207</td>
<td>0.29781</td>
</tr>
<tr>
<td>II</td>
<td>30</td>
<td>1.1957</td>
<td>0.61491</td>
</tr>
</tbody>
</table>

**Table 2. Mean Difference between IJV Lactate Levels in Group I and II**

Internal jugular vein lactate values measured and mean value calculated. The results obtained were used to calculate the mean difference between IJV lactate levels in each group (Table 2).

The difference between the two lactate values were found to be significant within group II compared to group I with a p-value <0.001 (Figure 1).
coefficient. In contrast to barbiturates, propofol is not antianalgesic.\textsuperscript{5-11} Propofol decreases Intracranial Pressure (ICP) in patients with either normal or increased ICP.\textsuperscript{12}

The decrease in ICP (30% to 50%) is associated with significant decreases in Cerebral Perfusion Pressure (CPP), however. The use of propofol in head injured patients should be restricted to doses providing mild-to-moderate sedation (i.e., blood concentration of 2 µg/mL, infusion of 25-75 µg/kg/min.).\textsuperscript{13} The lesser vasodilatory effects of propofol on the cerebral vasculature compared with volatile anaesthetics may provide advantages in certain surgical procedures.

The neuroprotective effects of propofol remain controversial. Propofol administered to burst suppression results in significantly better neurologic outcome and less brain tissue injury in an incomplete ischaemia model in rats compared with fentanyl.\textsuperscript{14} Propofol administered at sedative concentrations started either immediately after or at 1 hour after an ischaemic insult significantly reduced infarct size compared with awake controls infused with intralipid.\textsuperscript{15}

Sevoflurane is a fluorinated methyl isopropyl ether. The blood:gas partition coefficient of sevoflurane (0.69) resembles that of desflurane, thus ensuring prompt induction of anaesthesia and recovery after discontinuation of the anaesthetic. Sevoflurane is nonpungent, has minimal odour, produces bronchodilatation similar in degree to isoflurane and causes the least degree of airway irritation among the currently available volatile anaesthetics. Sevoflurane metabolism does not result in the formation of trifluoroacetylated liver proteins (as occurs with all other volatile anaesthetics). Sevoflurane does not form significant amounts of carbon monoxide on exposure to carbon dioxide absorbents. In contrast to other volatile anaesthetics, sevoflurane breaks down in the presence of the strong bases present in carbon dioxide absorbents to form compounds that are toxic in animals (compounds A).

Cerebral Blood Flow (CBF) autoregulation can be defined as the maintenance of constant cerebral perfusion during changes in Cerebral Perfusion Pressure (CPP). The mechanism of CBF autoregulation is still not completely understood, but myogenic, metabolic, neurogenic and endothelial factors seem to be involved. CBF autoregulation is mediated through vasodilation or vasoconstriction at the level of the resistance vessels, although changes in vascular tone of large cerebral arteries may shift the regulatory range. In rodents and humans, the autoregulatory range is within CPP values of approximately 60-150 mmHg.\textsuperscript{16-19}

Volatile anaesthetics produce direct cerebral vasodilation and increases in CBF in a dose-dependent fashion. In rats, CBF is increased with higher concentrations (1.7-2.0 MAC) of halothane, isoflurane and sevoflurane. This is consistent with data in humans, in which sevoflurane increased CBF as a result of a dose-dependent reduction in Cerebrovascular Resistance (CVR).\textsuperscript{20} Consequently, pharmacological cerebrovascular dilation (i.e., low baseline cerebrovascular tone) induced by higher concentrations of volatile anaesthetics may further impair autoregulatory decreases in CVR. Autoregulation of CBF is a function of changes in CVR.
in response to changes in CPP. This mechanism is sensitive to the status of the individual baseline cerebrovascular tone. If CBF autoregulation is intact, CBF remains constant as CPP changes.

Several studies have shown dose-dependent changes in CBF autoregulation with volatile anaesthetics.

Oxygen-free radicals cause brain injury associated with trauma and stroke. These reactive oxygen species maybe detoxified by endogenous antioxidants, but cell death occurs after antioxidants become depleted. General anaesthetics penetrate into brain parenchyma, where they may abrogate oxidative injury to neurons by several mechanisms that prevent the initiation of free-radical chain reactions or terminate the propagation of highly-reactive radicals. General anaesthetics may inhibit free-radical generation, because these drugs slow cerebral utilisation of glucose, inhibit oxidative metabolism in neutrophils and prevent redox changes in haemoglobin.21,24

Sevoflurane and propofol anaesthesia protect the brain from incomplete or focal cerebral ischaemia. The protective effect of these drugs may be related to their ability to suppress sympathetic activity and the stress response related to hypotension and ischaemia. Circulating catecholamines have been implicated in neuronal injury during incomplete ischaemia and the mechanism of injury maybe due to increased cerebral metabolic activity. Increased brain tissue excitatory neurotransmitters have also been suggested to worsen brain ischaemic injury.22-24,15

Propofol (2, 6-disisopropylphenol) is an IV anaesthetic and sedative that dose-dependently increases the survival of brain cells and enhances neurologic outcome in experimental stroke. Propofol's structure differs from other hypnotic sedatives, but resembles the native antioxidant tocopherol (vitamin E) in containing a phenolic hydroxyl group. This moiety scavenges free radicals and inhibits lipid peroxidation. Propofol restores glutamate transport rate in astrocytes that have been oxidatively stressed by tert-butyl hydroperoxide (t-BOOH) (a cell-permanent alkyl peroxide that causes lipid peroxidation). Virtually complete protection of glutamate transport activity was achieved when propofol was administered simultaneously with t-BOOH and partial protection was observed when propofol was delayed 30 mins. after t-BOOH.

Sevoflurane (Sevorane) is fluoromethyl 2.2.2-trifluoro-1-(trifluoromethyl) ethyl ether. The low solubility of sevoflurane in blood and other tissues provide for rapid induction of anaesthesia, rapid changes in anaesthetic depth following changes in delivered concentration and rapid emergence following discontinuation of administration. Approximately, 3% of absorbed sevoflurane is biotransformed. Sevoflurane is metabolised in the liver by CYP2E1 with the predominant product being hexafluoroisopropanol. Hepatic metabolism of sevoflurane also produces inorganic fluoride. Serum fluoride concentrations peak shortly after surgery and decline rapidly. In a study done by Lu et al, CBF autoregulation was maintained with 1 MAC sevoflurane, whereas 2 MAC sevoflurane impaired the autoregulatory response to graded hypotension. The data support the view that the extent of autoregulatory vasodilation is an immediate function of the pre-existing baseline cerebrovascular tone that determines the vasodilatory capacity. However, the decrease in CBF with haemorrhage does not necessarily induce cerebral hypoperfusion as the baseline CBF should be significantly higher with 2 MAC sevoflurane compared with 1 MAC sevoflurane or fentanyl/NO.

Anaerobic metabolism of glucose by glycolysis is more with IV agents maintaining anaesthesia. This implies that inhalational agents maybe beneficial in maintaining cerebral blood flow reducing anaerobic metabolism of glucose and thereby reducing lactate production. There are no oxygen stores in the brain in contrast to myoglobin, which stores oxygen in the muscle. Thus, the rate of oxygen delivery from the blood to brain tissue critically depends on the vessel-to-tissue oxygen partial pressure (P\text{to}_2) gradient and the efficiency of oxygen transfer from the capillary bed. Recent investigations on lactate kinetics and oxygenation using lactate isotopes demonstrate simultaneous lactate uptake and release in the brain. In addition to glucose and ketone bodies, lactate is also known to be an essential part of cerebral energy metabolism. Recent trials have shown that the glucose taken up by astrocytes is converted to lactate and that the lactate released from astrocytes maybe taken up by neurons and used as energy, especially in activated neurons referred to as the astrocyte-neuron lactate shuttle hypothesis. Thus, partial metabolic compartmentalisation appears to exist between astrocytes and neurons with astrocytes feeding the neurons with lactate generated from glycolysis upon cerebral activation.25-18

CONCLUSION

- In conclusion, there is increased net cerebral lactate efflux with IV agents maintaining anaesthesia. Alterations in cerebral blood flow and cerebral ischaemia are lesser with sevoflurane and fentanyl maintaining anaesthesia compared with propofol and fentanyl.
- Propofol anaesthesia produces cerebral vasoconstriction under baseline conditions in relation to its ability to decrease cerebral oxygen consumption.
- Sevoflurane may enhance collateral perfusion during ischaemia because of its cerebrovasodilatory effects.

REFERENCES


