

Original Article

EFFECT OF LOW CONCENTRATION ISOFLURANE WITH THIOPENTAL SODIUM FOR CRANIOTOMIES OF INTRACRANIAL SPACE OCCUPYING LESION

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ABSTRACT

The primary objective of anaesthesia is to facilitate surgery at minimal risk to the patient and to ensure safe optimal recovery following the procedure. The minimal risk to the neurosurgical patient can be achieved with meticulous attention to the detail of intraoperative systemic and brain homeostasis. Safe early recovery from craniotomy necessitates an anaesthetic technique pharmacology adequate to permit early awakening. The present study was designed to observe the effect of different anaesthetic technique that permits early recovery and hemodynamic stability. A total number of thirty patients both male and female age range 18 to 60 yrs having ASA grade-I & II and were randomly selected. They were equally divided into two groups. Group A received TPS infusion and group B received isoflurane inhalation with low dose of TPS infusion. Other drugs remained same for both group. Group A Received induction dose of TPS 4 – 5 mg/kg, maintained by TPS (4 – 5 mg/kg/h infusion), fentanyl (3 mgm/kg bolus, 1 - 2 mgm/kg/h infusion), oxygen/N₂O mixture FiO₂ being 0.3. Group B- Received induction dose of TPS 4 – 5 mg/kg and maintained by isoflurane 0.5%, oxygen/N₂O mixture FiO₂ being 0.3, fentanyl (3 mgm/kg bolus, 1 - 2 mgm/kg/h infusion), and low dose TPS (1 - 2 mg/kg/h) infusion.

In all patients induction was done with TPS 4 - 5 mg/kg and vecuronium (0.1 mg/kg) was used for tracheal intubation, muscle relaxation was maintained by vecuronium 0.01 mg/kg intermittently. Both groups received midazolam

(0.1 mg/kg), lignocaine 1.5 mg/kg 2 minutes before induction. Both groups received frusemide 1 mg/kg just after induction and mannitol 1 gm/kg when scalp incision was given. Anaesthetic procedure was performed with monitoring of hemodynamic variable pulse, blood pressure, SPO₂, E_TCO₂, temperature, urine output. Hemodynamic variable pulse, blood pressure were measure before induction, at intubation, every 15 min. interval and before extubation. Data were analyzed by paired and unpaired student's t-test as appropriate using SPSS software. Hemodynamic response to intubation does not differ significantly between the two groups. But it was observed that at intubation in both groups the pulse and mean arterial blood pressure was raised in compare to baseline, which gradually came down as anaesthetic depth increased and then remained stable all through the procedure.

Recovery was evaluated using Aldrete score. Total score significantly differ between two groups up to 30 min after extubation. Group A showed delay recovery up to 30 min in compare to group B. But after 30 min there was no significant difference in scoring between two groups. Total cost of main anaesthetic agent used significantly lower in group A. This study showed that the total infusion of TPS technique was as equally effective as using low concentration of isoflurane with conjunction of low dose TPS regarding perioperative hemodynamic stability. But the cost was minimal in thiopental sodium infusion group with the expense of a little bit delayed recovery.

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INTRODUCTION

The primary objective of anaesthesia is to facilitate surgery at minimal risk to the patient and to ensure optimal recovery following the procedure. General anaesthesia can be regarded as a 'quadrate' of the hypnosis, analgesia, muscle relaxation and amnesia. To achieve these effects, a combination of therapeutic agents is administered in the practice known as balanced anaesthesia. The hypnosis, analgesia, muscle relaxation could now be produced by separate agents without the cardiovascular risk of providing all three with the same technique deep inhalation anaesthesia or extensive regional technique¹.

At present there are different surgical procedures that are being performed under different kind of anaesthesia. Different procedures have different anaesthetic goals and techniques. Researchers are continuously looking for better anaesthesia by improving the quality of drugs, instruments and different procedures to provide a safe landing from anaesthesia and good operative condition. Anaesthesia for neurosurgical procedures also needs some special technique and maneuver. Major goals in neurosurgical anaesthesia are to provide adequate tissue perfusion to the brain (and spinal cord) so that the regional metabolic demand is met and adequate surgical conditions (a "relaxed brain") is provided. If anaesthetic drugs or anaesthetic techniques are improperly used, they can worsen the existing intracranial pathologic condition and may produce new damage. Some anaesthetics or anaesthetic techniques may help protect the brain subjected to metabolic stress or even ameliorate damage from such an insult².

Neuroanaesthetic procedure for surgery of intracranial space occupying lesion (ICSOL) is a major component of neuroanaesthesia. About 60% of all brain tumors are primary and supratentorial, and the most common ones presented by adults are gliomas, astrocytomas, oligodendrogliomas (≈35%), meningiomas (≈15%), and pituitary adenomas (≈8%)³. For patients the problems associated with intracranial tumors result from local and generalized pressure, whereas for surgeons the difficulties arise during surgical exposure, as the brain is particularly susceptible to retraction and mobilization damage. Anaesthesia for intracranial space occupying lesion (ICSOL) thus requires an

understanding of the pathophysiology of localized or generalized rising intracranial pressure (ICP); the regulation and maintenance of intracerebral perfusion; the effect of anaesthesia on ICP, perfusion, and metabolism; and the therapeutic options available for decreasing ICP, brain bulk, and tension perioperatively. Specific problems include massive intraoperative hemorrhage, seizures, and air embolism in the head-elevated or sitting position or if venous sinuses are traversed. Further questions are how to monitor the brain's function and environment and whether to aim for rapid anaesthetic emergence or for prolonged post operative sedation and ventilation. Finally, the concurrence of various intracranial or extracranial pathologic conditions should not be forgotten, such as presence of cardiovascular or pulmonary disease or in case of metastases the existence of paraneoplastic phenomena and the effects of chemotherapy or radiotherapy should also be considered.

At present, the major argument for the still extensive and successful use of volatile-based technique remains the controllability, predictability, and attainability of early awakening⁴. However, the increasing consensus is that, volatiles are otherwise far from ideal agents for neuroanaesthesia because of their ability to increase cerebral blood flow (CBF), ICP, and brain bulk⁵⁻⁷. Although intravenous technique offer good control for CBF, ICP, and brain bulk⁸⁻¹¹, prolonged or unpredictable awakening remains the main concern with intravenous technique, with possible resulting difficulties in the differential diagnosis of delayed awakening and the need for emergent CT scanning to rule out surgical complication.

Volatile anaesthetics such as halothane, sevoflurane, isoflurane are commonly used in neuroanaesthesia. Among these agents isoflurane seems to more neurofriendly as because it increase CBF, and ICP to a lesser extent than halothane or sevoflurane, while cerebro-metabolic rate of oxygen (CMRO₂) reduces significantly^{5-7,12}. But isoflurane is a very costly agent as compared to other volatile agents at present available here.

Among intravenous anaesthetics agents' thiopental sodium (TPS) and propofol, are used commonly. Both agents make a favorable condition of brain for ICSOL surgery as both reduces CBF, ICP, CMRO₂, and also gives some cerebral protection from focal

cerebral ischemia, but it seems that there are delayed awakening while using thiopental sodium, while it is early in case of propofol¹¹.

In Bangladesh, many neurosurgical procedures are being performed. Traditionally the volatile anaesthetic agent used is halothane, which does not provide a desirable neuroanaesthetic condition and thiopental sodium acts as intravenous anaesthetics counterpart. Recently isoflurane have become available here, though it is very expensive. The recommended concentration for maintaining general anaesthesia seems to be outweigh the otherwise claimed benefit. To improve the present anaesthetic status in intracranial surgery isoflurane looks quite attractive, but at the same time TIVA, one of the alternative technique has already got good grounds⁴. But this technique suffer from the problem associated with delayed awakening which makes difficulties in early neurological assessment to rule out any surgical complication. Literature survey does not reveal any work on below 1 MAC isoflurane with combination of infusion anaesthetic agent. This study was done with isoflurane in a low concentration to avoid the deleterious effect of increased ICP and to reduce cost. This may be helped by adding an intravenous infusion of low dose TPS to compensate using low conc. isoflurane with the aim to achieve a good operating condition for the surgical procedure, stable hemodynamic and quick recovery of the patient and compare it with total infusion of TPS.

MATERIAL AND METHOD

Study Population

Total 30 patients with different neurosurgical problem with intracranial space occupying lesion for craniotomy under general anaesthesia were selected for the study. Both male and female patient within age group 18 - 60 years were selected. They were recruited and grouped randomly by blind envelope method. 30 envelopes of which 15 for group-A and 15 for group-B were kept in a box. Patient was asked to pick up one envelope randomly from that thirty pre fixed envelope to be assigned in one group. The purpose of the study, methodology, complications, side effects of each method of anaesthesia were clearly explained to each of the subject and recruited only after they had given written consent. The approval of the University Departmental Ethics Committee was duly taken before carrying out the study.

Grouping of Patients

Group A – Received induction dose of TPS 4 – 5 mg/kg, maintained by Thiopental (4 - 5 mg/kg/h infusion), Fentanyl (3 mgm/kg bolus, 1 mgm/kg/h infusion), oxygen/N₂O mixture FiO₂ being 0.3. Group B – Received induction dose of TPS 4 – 5 mg/kg, maintained by isoflurane 0.5%, oxygen/N₂O mixture FiO₂ being 0.3, Fentanyl (3 mgm/kg bolus, 1 mgm/kg/h infusion), and low dose TPS (1-2 mg/kg/h) infusion.

PROCEDURES

Preoperative Management

After obtaining the permission and the informed consent of the patient this study was performed. Preanaesthetic assessment was done on the previous day of surgery. Preanaesthetic assessment attempted to establish the neurologic and general state of patient. Preanaesthetic history of headache, nausea, vomiting, blurred vision evaluated to establish the presence of intracranial pressure. History of seizure, decreased level of consciousness, somnolence, hemiparesis, and sensory deficits are noted. Medication history was noted because concurrent medicine also affects intracranial compliance, perfusion and reserve as well as recovery. Examination included general examination, cardiovascular, respiratory renal, hepatic, endocrine and nervous system. Examination included neurological assessment documenting mental status and existing sensory or motor deficit. Neurological status comprising ability follows commands, patient's degree of orientation, presence or absence of speech deficit and the Glasgow Coma Score.

Medication was reviewed with special reference to corticosteroid, diuretics and anticonvulsants. Laboratory investigation included complete blood counts, hematocrit, X ray chest, ECG, blood glucose, blood urea, serum creatinine, urine for R/E. Laboratory investigation evaluated to rule out corticosteroid induced hyperglycemia and electrolytes disturbances due to diuretics. Computerized tomography and magnetic resonance images reviewed for evidence of brain edema. Evidence of midline shift of the brain (greater than 0.5 cm) on computed tomography also suggests the presence of increased ICP.

Preoperative medication

Preoperative medication that produces sedation or ventilatory depression was avoided in the patient with intracranial tumor. In case of tumor with no clinical or other sign of increase ICP, a small dose benzodiazepines 5 mg midazolam orally was used to decrease the level of anxiety. Steroid continued on the morning of operation 4 mg/i.v dexamethasone. For longer-term steroid treatment with probable pituitary axis suppression, stress coverage was provided by 100 mg methyl prednisolone.

Intra-operative Management

Patient was identified and preanaesthetic assessment was reevaluated. Size and position of the tumor, the tissue diagnosis, the surgical approach, the structures in proximity and likelihood of their involvement by surgery, and whether the tumor is to be removed radically, age, physical status, predictable intraoperative blood loss, position during surgery was considered before induction of anaesthesia.

A large bore intravenous catheter was placed as were electrocardiogram leads, blood pressure cuff, pulse oximeter and capnometer. Bladder catheterization was done. Ventilatory control (avoidance of hypercapnia and hypoxemia, early establishment of mild hyperventilation), sympathetic and thus blood pressure control (adequate depth or an anaesthesia and antinociception to prevent CNS arousal), and prevention of cranial venous out flow obstruction (head positioning) were considered for induction of anaesthesia.

Before induction of anaesthesia patient breathed 100% oxygen for three minutes.

If patient seems to be light as indicated by heart rate >100 and sweating then TPS infusion was increased at the discretion of attending anaesthesiologist to bring heart rate <100.

In all patients induction was done with TPS 4 - 5 mg/kg and vecuronium (0.1 mg/kg) was used for tracheal intubation, muscle relaxation was maintained by vecuronium 0.01 mg/kg intermittently. **Group A** patients were maintained by TPS (4 - 5 mg/kg/h infusion), fentanyl (3mgm/kg bolus, 1-2 mgm/kg/h infusion), 30% N₂O in O₂. **Group B** were maintained by isoflurane 0.5%, 30%

N₂O in O₂, fentanyl (3mgm/kg bolus, 1-2 mgm/kg/h infusion), and low dose TPS (1-2 mg/kg/h infusion). Both groups received midazolam (0.1 mg/kg), lignocaine 1.5 mg/kg 2 minutes before induction. Both groups received frusemide 1 mg/kg just after induction and mannitol 1 mg/kg when scalp incision was given. Ventilation was adjusted to maintain E_TCO₂ at 28 - 30 mmHg in both groups. Intraoperative hypertension (B.P >20% of baseline) was managed by Glyceryl trinitrate (GTN) (0.5 - 1 mgm/kg/min) infusion. In both groups at the end of procedure when dural stich was finished then TPS and fentanyl infusions were stopped. Isoflurane was stopped about 20 min before the end of the procedure. Patients were reversed with neostigmine (0.05 mg/kg) and atropine (0.015 mg/kg) and extubated when adequate spontaneous ventilation was established.

Preoperative intravascular deficit was estimated with duration of fast. The deficit was estimated by multiplying the normal maintenance rate by the length of fast. Normal maintenance fluid requirement was estimated as follows. For the first 10 kg, 4 ml/kg/h, for next 10 - 20 kg, 2 ml/kg/h for each kg, above 20 kg- 1 ml/kg/h. Abnormal fluid losses due to vomiting, diuresis, diarrhoea, blood loss and fever was considered. Intravascular fluid volume depletion due to blood loss was corrected with the whole blood. Intraoperative maintenance fluid considered was normal saline solution. Recovery from anaesthesia was assessed by Aldrete Score.

Dural condition and tension were measured by subjective assessment of the surgeon. Tension of dura would be used as a guide. When the dura was opened then the surgeon was asked to provide an assessment of the condition of the brain. This was done using a four- point scale developed by Todd *et al.*¹³,

1= excellent, no swelling; 2= minimal swelling but acceptable; 3= serious swelling but no specific change in management required; 4= sever brain swelling requiring some intervention, such as a change in position, a further reduction in PaCO₂, additional mannitol, or furosemide. After reversal patients were assessed with Aldrete post-anaesthetic recovery score (Annexe-A), every 10 minutes interval for one hour.

All information was collected in a spreadsheet format, and data were analyzed by student's "t" test (paired and un-paired as appropriate) using 'SPSS' software.

P < 0.05 was considered as significant.

OBSERVATION AND RESULTS

Demographic characteristics of patients

No differences were found between groups with regard to demographics.

The age, sex and weight are presented in Table-I. The median age (range) in year 38 (18 - 55) in group A and 40 (18 - 60) in group B. The weight (mean \pm SEM) in kg were 57.00 ± 2.11 in group A and 52.00 ± 1.87 in group B.

Age and weight are almost similar in two groups.

Table I

Age, sex and weight distribution of the study subjects

	Group A	Group B
No of patients (n)	15	15
Sex (Male/Female)	11/4	9/6
Age, Median (range) in year	38 (18 - 55)	40 (18 - 60)
Weight, (mean \pm SEM) in Kg	57.00 ± 2.11	52.00 ± 1.87

Hemodynamic Values

The study showed there was no significant difference between two techniques regarding hemodynamic stability. In both groups the pulse and mean arterial blood pressure was increased from base line value during induction and intubation. But as the anaesthetic depth increased these value gradually came down and then remained stable throughout the intraoperative period. Pulse before operation, at intubation, during maintenance of anaesthesia and before extubation was shown in Figure 1. Mean arterial pressure preoperatively, at intubation, during maintenance of anaesthesia and before extubation was shown in Figure 2.

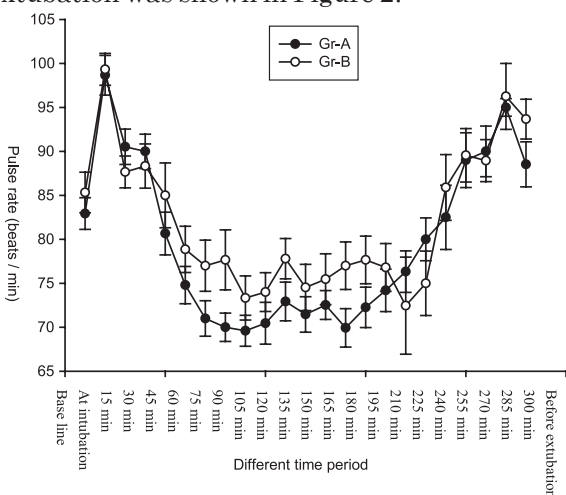


Fig.-1: Changes of pulse rate in two groups at different time period

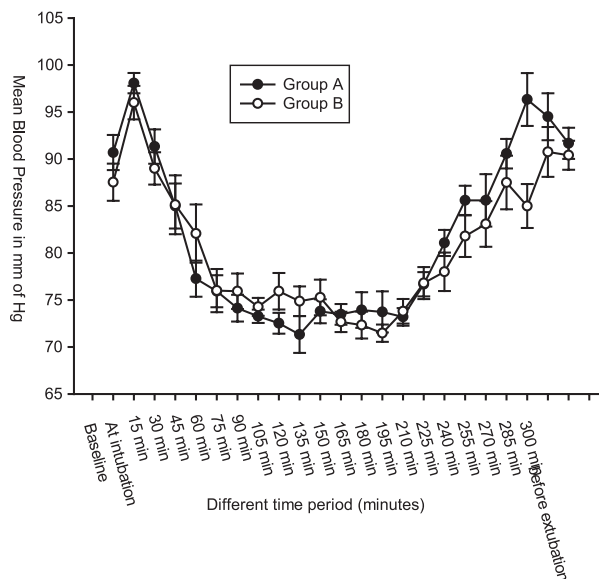


Fig.-2: Changes of mean arterial blood pressure in two studied groups at different time period Dural condition

The surgeon at the opening of the bone flap assessed dural condition. There was no significant difference of the dural tension and condition between the two groups.

Table II

	Group A	Group B	P value
Score of Dura	1.33 ± 0.12	1.26 ± 0.11	0.702

Data are presented as mean \pm SEM. Between groups, unpaired t test was performed.

RECOVERY

After extubation neurologic status was assessed repeatedly and recorded. Assessment consisted with Aldrete post anaesthesia score. Patients were evaluated every 10 min until a normal score 9 - 10 obtained when the patients were regarded awake and alert, oriented, responding to commands, and normal motor function. In terms of neurological assessment patients with score below 9 shows some signs of drowsiness, partially co-operative and partially awake.

Recovery score from anaesthesia using Aldrete recovery score every 10 min interval for 60 min from extubation were shown in Table - III

Table-III

Aldrete recovery score every 10 min interval for 60 min from extubation

Time in min.	Group A	Group B	P value
10 min.	7.13 ± 0.236	8.73 ± 0.238	0.001
20 min.	8.60 ± 2.890	9.90 ± 0.066	0.001
30 min.	9.53 ± 0.165	10.00 ± 0.000	0.009
40 min.	9.93 ± 0.066	10.00 ± 0.000	0.326
50 min.	10.00 ± 0.000	10.00 ± 0.000	-
60 min.	10.00 ± 0.000	10.00 ± 0.000	-

Data are presented as mean ± SEM. Between groups, unpaired t test was performed.

The mean Aldrete score significantly differ among group A and group B upto 30 min from extubation.

The Aldrete score at every 10 min interval were, at 10 min 7.13 ± 0.236 vs 8.73 ± 0.238, at 20 min. 8.60 ± 2.89 vs 9.90 ± 0.066, at 30 min. 9.53 ± 0.165 vs 10 ± 0.000. These values showed significant difference between the two groups.

Total TPS used

Total TPS used in group A naturally significantly higher then group B. But it was observed that very low dose TPS used in conjunction with isoflurane in group B with stable hemodynamic status during maintenance of anaesthesia.

Total cost of used TPS and isoflurane (in Taka)

Table-IV

Total cost of used main anaesthetics agents (TPS and isoflurane)

	Group A	Group B
Isoflurane	—	2000
TPS	195	65
Total	195	2065

Total cost of used main anaesthetic agents (TPS and isoflurane) significantly differs between two groups because of higher cost of isoflurane.

DISCUSSION

Anaesthesia, the gateway to surgery, its successful exit ends with safe recovery. Recovery from

anaesthesia has respiratory, cardiovascular, metabolic, endocrine and neurologic consequence¹⁴. Ideally patient recovery from neurosurgery should emerge rapidly from anaesthesia to permit immediate assessment of the result of surgery and to provide base line for continuing postoperative neurologic follow-up¹⁵. Different anaesthetic agents have different effects on cerebrovascular physiology. However- the importance of these differences in neuroanaesthetic practice is unclear. In general volatile anaesthetic are far from ideal agents for neuroanaesthesia because of their ability to increase CBF, ICP and brain bulk⁵⁻⁷. Adams⁶, showed the effect of Isoflurane on cerebral fluid pressure (CSFP) in patients undergoing craniotomy for intracranial supratentorial neoplasm or hepatoma. He used 1% isoflurane in two groups of patients. One group maintained hypocapnia and other group maintained normocapnia. He found that CSFP did not increase in hypocapnic group but in the normocapnic patients CSFP consistently increased. Although intravenous technique offer good control for CBF, ICP, and brain bulk⁸⁻¹⁰. Van¹⁰, found in one study that propofol 2.5 mg/kg in bolus injection does not increase ICP but can produce a significant decrease of the cerebral perfusion pressure due to a marked decrease in mean arterial pressure in patients with a brain tumor. Prolonged or unpredictable awakening remains the main concern with intravenous technique, with possible resulting difficulties in the differential diagnosis of delayed awakening and the need for emergent CT scanning to rule out surgical complication.

Present study compared total TPS infusion based anaesthesia technique with low concentration isoflurane supplemented by low dose infusion of TPS anaesthesia in resection of supratentorial intracranial mass in relation to hemodynamic stability and recovery, which are desirable in intracranial surgery.

The study showed there was no significant difference between two techniques regarding hemodynamic stability. In both groups the pulse and mean arterial blood pressure was increased from base line value during induction and intubation. But as the anaesthetic depth increased these value gradually came down and then remained stable throughout the intraoperative period. These findings are similar to many previous studies^{2,13,16}. Van *et al*¹¹, studied

two anaesthetic technique, where in one group anaesthesia induced with thiopental sodium, fentanyl and maintained with fentanyl, dehydrobenzperidol, isoflurane, nitrous oxide, and a thiopental sodium infusion. Other group anaesthetized with propofol loading infusion followed by a maintenance infusion at a fixed rate. They found significant increase in mean arterial blood pressure and pulse during intubation with thiopental group but did not change in propofol group.

But it was observed in the present study that pulse rate in isoflurane group were a little bit higher than TPS group throughout the intraoperative period, although not significantly different between two groups, which is similar to the study done by Todd *et al.*¹³, when he used propofol/fentanyl, isoflurane/nitrous oxide, fentanyl/nitrous oxide. He observed increased pulse rate in the intraoperative period in isoflurane group, though it was not significantly different to other groups. Many previous studies^{13,16} also showed that there were no significant differences regarding hemodynamic stability when using different anaesthetic techniques. Towards the end of anaesthesia in both groups pulse and mean arterial pressure were gradually increased though there was no significant difference between two groups. This increased pulse and mean arterial blood pressure may be due to lack of anaesthetic agents and patient become lighter as the anaesthetics were discontinued when the dura was closed. From dural closer to head dressing approximate elapsed time about 30 min to 45 min. This finding was also seen in one study¹⁶ where propofol infusion, isoflurane inhalation, and combined propofol and isoflurane were used. But in another study¹⁷ where propofol, isoflurane used showed propofol group had a more stable pulse and blood pressure than isoflurane group. These variations may be due the differences in dose and type of the anaesthetics agents used.

Present study also observed dural tension when the bone flap was removed. It was found that dura was relaxed enough to perform surgery comfortably in both groups. There was no significant difference between two groups regarding dural tension. It was similar finding as found in one study¹³ where anaesthetics used- propofol/fentanyl, isoflurane/N₂O, fentanyl/N₂O. But in another study¹⁸⁻¹⁹ found that the dural tension was significantly lower

in propofol group then isoflurane group but not sevoflurane group. The difference between the groups was presumed to be caused by differences in the degree of vasoconstriction elicited by the anaesthetics.

Recovery is one of the key factor of standard neuroanaesthetic procedure. Present study evaluated recovery from anaesthesia using Aldrete recovery score every 10 min interval for 60 min from extubation of patient. It showed significant difference in recovery score between the two groups. Group A showed delayed recovery score (score <9) up to 20 min then group B but after 30 min there was no significant difference in recovery score. In group B recovery score <9 for about 10 minute, this differences was may be due to using low concentration of isoflurane with a background of very low dose infusion of TPS. So that the residual effect of anaesthetics wearied off very quickly and recovery was faster which is desirable.

Although many previous studies showed no significant difference in recovery using different types of anaesthetics^{2,13,16}.

Though the present study was not a health economic investigation. Using current cost of one bottle (100 ml) isoflurane taka 3000/- and one vial TPS (500 mg) taka 65/-. It was estimated that a patient with average weight and average duration of surgery anaesthesia cost in group A of TPS 3 vial taka 195/- and in group B of isoflurane 2000/-(1 bottle contain 100 ml liquid isoflurane, costing TK.3000/- and at a concentration of 0.5%, the average total isoflurane used was estimated as 60 ml at 15 ml/h) + 1 vial TPS 65/-. Anaesthesia with isoflurane was costly then TPS. Time to discharge from recovery room was earlier with isoflurane. This provides advantage of short duration stay in recovery room with isoflurane. ICU management and ventilator support with delay was minimized with the use of low concentration isoflurane supplemented by low dose TPS infusion, which may impact in reducing total cost by isoflurane.

CONCLUSION

Low concentration of isoflurane with low dose TPS infusion has been found quite effective and showed better recovery compared to total TPS infusion technique. But in terms of cost benefit, use of TPS technique has come out lot cheaper.

Although there are modest differences between the two tested anaesthetics, short-term outcome was not affected. These results indicate that, despite their respective cerebrovascular effects, all of the anaesthetic regimens used were acceptable in these patients undergoing elective intracranial surgery.

Low concentration isoflurane technique can be recommended for further studies for surgery with large intracranial mass where fear of neuronal damage exists by manipulating brain tissue peroperatively and early recovery needed to evaluate neurological status early postoperatively.

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