Propofol Requirement during Propofol and Butorphanol Anesthesia with and without Nitrous Oxide in Short Duration Intracranial Surgeries: A Bispectral Index Guided Study

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Abstract

Introduction: Propofol is a preferred agent in neurosurgical anesthesia because of its favorable effects on cerebral hemodynamics and excellent recovery profile. Butorphanol is a synthetic opioid which is 5-8 times more potent than morphine and is known to provide stable hemodynamics during various surgical procedures. Owing to its unfavorable effects on cerebral metabolism and hemodynamics nitrous oxide has a debatable role in neurosurgical anesthesia. But studies on exact dose requirement during propofol induction and maintenance anesthesia along with butorphanol with and without the use of N2O during craniotomies are lacking. So we aimed at studying the requirement of propofol (used along with butorphanol) with and without the use of nitrous oxide in intracranial surgeries using bispectral index (BIS) monitoring.

Material and methods: Fifty ASA grade I/II patients (16-60 years) scheduled for elective intracranial surgeries (≤ 4 hour duration) were included and were randomly allocated into two groups, group P and PN. All received IV midazolam and butorphanol at a dose of 30 µg/kg each. Anesthesia was induced with propofol and maintained on propofol with oxygen in air (1:1 ratio) in group P and nitrous oxide in oxygen (2:1 ratio) in group PN patients. BIS score of ≤ 40 at the time of endotracheal intubation, 50-60 during maintenance and ≥ 70 at extubation was maintained. The overall and maintenance dose requirement of propofol and the recovery profile were studied.

Results: The overall and maintenance propofol doses were significantly higher in group P than group PN (100.02 ± 20.28 µg/kg/min Vs 79.62 ± 13.13µg/ kg/min; p<0.001) and (90.82 ± 19.13 Vs 71.26 ± 11.78 µg/kg/min; p<0.001) respectively. The recovery profiles were identical between groups.

Conclusion: When used along with butorphanol the overall and maintenance doses of propofol without the use of nitrous oxide are 100.02 ± 20.28 µg/ kg/min and 90.82 ± 19.13 µg/ kg/min respectively which is more (p<0.001) than the dose required in combination with nitrous oxide (79.62 ± 13.13 and 71.26 ± 11.78 µg/kg/min respectively).

Abstract: Neurosurgical anesthesia; Nitrous oxide; Bispectral index

Introduction

Propofol is a preferred intravenous agent neurosurgical anesthesia due to its favourable effects on neurophysiology. It causes a dose dependent decrease in intracranial pressure maintaining cerebral perfusion at modest doses. Furthermore it causes a reduction in cerebral metabolic rate (CMR) without any disturbance in cerebral reactivity to carbon dioxide and autoregulation [1]. Nitrous oxide (N2O) is less preferred anesthetic agent in current neurosurgical anesthesiology practice due to its unfavorable effects on neurophysiology. It is widely acclaimed to have a controversial role, especially in settings of raised intracranial pressure [1].

Single dose butorphanol is reported to provide better intraoperative hemodynamics and recovery when used with propofol during neurosurgery [2]. Butorphanol has also been reported to provide adequate analgesia when used as a supplement in balanced anesthetic technique [3] and at doses between 30-60 µg/kg butorphanol is reported to produce no or minimal cardiovascular changes [4]. Unfortunately, studies on exact dose requirement during propofol induction and maintenance anesthesia along with butorphanol with and without the use of N2O during craniotomies are lacking. Therefore, we aimed at studying the dose requirement of propofol (used along with butorphanol) with and without the use of N2O during craniotomies using bispectral index (BIS) monitoring.

Material and Methods

After obtaining the institutional ethical committee approval and written informed consent, 50 patients of ASA grade I/II, aged between 16-60 years scheduled for elective intracranial surgeries (for any supratentorial mass lesion) were included in this prospective randomized study. Patients with clinical or radiological features of raised intracranial pressure (ICP) or Glasgow Coma Scale Score of <15; those undergoing surgery for intracranial aneurysm, arterio venous malformation or infratentorial mass; those with psychiatric disorders, severe lung disease, coronary artery disease, hepatic or renal insufficiency, uncontrolled hypertension, obesity, history of alcohol or drug abuse or known allergy to the study drug; undergoing frontal craniotomy (inability to place BIS sensor frontally); history of craniotomy with in past 30 days; patients who were intubated for any reasons before the surgery; and pregnant and lactating women were excluded from the study. The patients were randomly allocated into two groups, namely propofol alone group-P (n=25) and propofol with...
N₂O group-PN (n=25) by draw of lots. To ensure an identical depth of anesthesia between the groups, we used bispectral index (BIS) monitoring (BIS XP monitor, A2000; Aspect Medical Systems Inc., Natick, MA) as a measure of depth of anesthesia.

Patients in both groups were premedicated with tab alprazolam 0.25 mg to 0.50 mg in the night before and on the morning of the day of surgery. In the operation theater BIS monitor (electrodes were placed according to the manufacturer’s specifications) and all the standard routine non invasive monitors were connected and baseline heart rate (HR), mean arterial blood pressure (MABP), Bispectral index (BIS) score, respiratory rate and oxygen saturation (SpO₂) were recorded in all patients. Patients in both groups received IV injection of midazolam (30 µg/kg) and butorphanol (30 µg/kg) 5 minutes before induction of general anesthesia (GA) and all were preoxygenated by oxygen mask at 6 litres/min for 3 minutes and GA was induced with propofol titrated to loss of verbal response. In all patients propofol infusion was started simultaneously with induction keeping a BIS score ≤ 40 until tracheal intubation (which was facilitated with vecuronium bromide 0.1 mg/kg IV). Following induction of GA central venous and intra-arteral cannulation were performed and anesthesia was maintained on propofol infusion using oxygen in air (1:1 ratio) in group P and N₂O in oxygen (2:1 ratio) in group PN. The pin insertion sites were infiltrated with 0.25% bupivacaine in all patients before application of skull pins. Intermittent doses of vecuronium bromide were repeated as per requirement. Maintenance dose of anaesthetics in both the groups were titrated to a BIS score of 50–60. Mechanical ventilation was adjusted to a PaCO₂ of 30 ± 2 mmHg and euvolemia and euthermia were ensured in all patients. Mean arterial pressure ≥ 20% above baseline was managed with ensuring adequate depth of anaesthesia and inj esmolol (0.5-1 mg/kg). Any fall in MABP to ≤ 20% of the baseline value, was managed with IV boluses of phenylephrine (100 µg boluses) after ruling out hypovolemia. Hypovolemia was treated with normal saline, managed with ensuring adequate depth of anaesthesia and inj esmolol (0.5-1 mg/kg). All the patients received inj granisetron (1 mg) IV and inj ketorolac (30 mg) IM 30 mins before conclusion of surgery.

The anesthesia in both groups continued until closure of head wounds/last skin suture. Residual of neuromuscular blockade was done with standard doses of neostigmine and glycopyrrolate IV. After obtaining BIS score of ≥ 70 and ensuring adequate spontaneous respiration and ability to protect airway, patients’ trachea were extubated and they were shifted to the post anesthetic care unit (PACU). After cessation of anesthetic agents time to open eyes (emergence time) and tracheal extubation (extubation time) were noted in all patients. Patients were observed for postoperative nausea and vomiting (PONV), respiratory insufficiency, need for ventilatory support and other side effects, if any, in the post operative period. The data were recorded as baseline, post premedication, immediate post induction and intubation, at pin fixation and thereafter at every 15 minute intervals till the stoppage of propofol and at 5 minute intervals till 15 mins after extubation (post extubation values).

### Statistical analysis

Considering the average of maintenance dose of propofol obtained from pilot study of 20 patients [Group P: 90.8 ± 19.13 µg/kg/min Vs Group PN: 75.2 ± 11.7 µg/kg/min] and a power of 90% and a error of 5% the sample size of our study was calculated to be 22 patients in each group which is in fact less than our actual study population (i.e. 25 patients in each group). Statistical analysis was done using windows SPSS software Version 12.0. The mean and standard deviation of the parameters studied were calculated for two groups and compared using unpaired ‘t’ test. The critical value of ‘p’ indicating the probability of significant difference was taken as <0.05.

### Results

Total 50 patients were enrolled in the study of which 8 patients were excluded because of need for elective post operative ventilation due to surgical reasons in 3 patients (3 in group P and 2 in group PN) and total duration of procedure exceeding the study duration in 3 patients (2 in group P and 1 in group PN). So data of 42 patients (group P=20 and group PN=22) were included for final analysis. The two groups were comparable in terms of mean age, weight, sex distribution and types of intracranial pathology (Table 1).

The inter-group comparison of HR and MABP at different time intervals is shown in Table 2. No significant difference of baseline HR and MABP were observed between the two groups. We observed a fall in both HR and MABP with respect to the baseline values following premedication and induction in both groups. The HR and MABP were higher than baseline values following intubation and pin insertion in both the group and the difference between the groups was insignificant

### Table 1: Demographic Data and type of intracranial pathology for the two groups of patients.

| Time Interval | Group P (n=20) | Group PN (n=22) | P Value |
|---------------|---------------|----------------|---------|
| MABP          | HR            | MABP           | HR      |
| Baseline      | 89.50 ± 8.08  | 83.30 ± 8.91   | 0.032   |
| Post Premedication | 89.50 ± 8.08  | 83.30 ± 8.91   | 0.032   |
| Post induction | 85.70 ± 7.53  | 80.70 ± 10.17  | 0.845   |
| Post Extubation | 94.5 ± 11.35  | 88.00 ± 16.11  | 0.827   |
| At pin fixation | 94.4 ± 11.35  | 86.0 ± 21.00   | 0.827   |
| T15           | 85.90 ± 9.11  | 83.20 ± 11.19  | 0.843   |
| T30           | 85.05 ± 9.70  | 84.25 ± 10.62  | 0.832   |
| T45           | 85.15 ± 8.91  | 85.65 ± 10.44  | 0.832   |
| T60           | 85.70 ± 9.91  | 85.75 ± 9.64   | 0.824   |
| T75           | 85.90 ± 9.22  | 85.89 ± 6.95   | 0.831   |
| T90           | 86.10 ± 8.58  | 87.10 ± 9.57   | 0.827   |
| T105          | 87.75 ± 7.83* | 86.50 ± 9.39   | 0.849   |
| T120          | 86.05 ± 7.66  | 87.55 ± 8.82   | 0.834   |
| T135          | 86.05 ± 7.52  | 86.00 ± 6.72*  | 0.841   |
| T150          | 87.89 ± 8.58  | 86.00 ± 7.39   | 0.832   |
| T165          | 87.74 ± 8.43  | 87.35 ± 9.43   | 0.832   |
| T180          | 87.47 ± 7.43  | 86.50 ± 8.72   | 0.843   |
| T210          | 95.00 ± 4.24  | 87.00 ± 12.73  | 0.866   |
| Mean Post extubation | 89.50 ± 4.76   | 88.16 ± 4.99   | 0.866   |

Significant difference was taken as <0.05.

The inter-group comparison of HR and MABP at different time intervals is shown in Table 2. No significant difference of baseline HR and MABP were observed between the two groups. We observed a fall in both HR and MABP with respect to the baseline values following premedication and induction in both groups. The HR and MABP were higher than baseline values following intubation and pin insertion in both the group and the difference between the groups was insignificant.

### Table 2: Comparison of mean arterial blood pressure (MABP) and heart rates (HR) between the two groups at different Time intervals.
Time Interval | Group P | Group PN | p-value
--- | --- | --- | ---
Baseline | 92.40 ± 2.54 | 93.73 ± 4.00 | NS
Post Premedication | 72.65 ± 9.54 | 75.82 ± 5.65 | NS
Post induction | 38.30 ± 4.92 | 38.77 ± 3.01 | NS
At Pin Fixation | 51.63 ± 3.22 | 52.3 ± 4.80 | NS
T15 | 50.35 ± 2.47 | 52.18 ± 4.13 | NS
T30 | 52.45 ± 2.14 | 52.55 ± 2.65 | NS
T45 | 54.50 ± 2.82* | 50.27 ± 4.87* | S (<0.001)
T60 | 53.70 ± 2.98 | 53.41 ± 3.54 | NS
T75 | 53.18 ± 3.24 | 51.69 ± 1.18 | NS
T90 | 55.20 ± 3.85* | 50.32 ± 5.04* | S (<0.001)
T105 | 53.05 ± 4.29 | 52.67 ± 2.48 | S (<0.001)
T120 | 57.10 ± 3.76 | 56.2 ± 3.27 | NS
T135 | 55.20 ± 3.04 | 53.55 ± 2.86 | NS
T150 | 58.50 ± 0.71 | 58 ± 1.1 | NS
T165 | 52.68 ± 4.03 | 52.95 ± 2.14 | NS
T180 | 56.10 ± 2.99 | 56.09 ± 2.73 | NS
T195 | 54.64 ± 4.20 | 53 ± 3.34 | NS
T210 | 55.05 ± 4.35* | 56.14 ± 4.90* | S (<0.001)

T15-T210 denotes the interval of time following pin fixation
*Significant difference (p<0.01)

Table 3: Comparison of Mean BIS values at different time intervals between two groups.

The HR was significantly higher in group P than group PN only at 75 and 135 mins after pin insertion whereas, the MABP was significantly higher in group P than group PN only at 105 mins after pin insertion. During rest of the period in the maintenance phase the difference of HR and MABP was insignificant. In our study 3 patients each in two groups required phenylephrine where as 5 patients in group P and 4 patients in group PN required esmolol. We did not find any event of hypoxemia in any of our patients. An inter-group comparison of BIS scores is shown in Table 3. The mean baseline BIS scores were similar in both groups. There was an identical fall in BIS scores in both groups after premedication with midazolam and butorphanol. There BIS scores were significantly higher in group P than group PN only at 45,90 and 210 minutes following pin fixation.

The mean duration of anesthesia, overall and maintenance propofol dose requirements, and mean emergence and extubation time are shown in Table 4. The mean anesthesia duration was identical in both groups (187.25 ± 16.47 mins Vs 176.59 ± 17.89 mins; p>0.05). However, the maintenance and overall mean dose requirements of propofol were significantly higher in group P than group PN (P<0.001). Though the mean emergence and extubation time appeared higher in group PN than group P (4.75 ± 1.7 mins Vs 4.42 ± 1.33 mins; p>0.05 and 8.50 ± 1.54 mins vs 7.5 ± 2.35 mins; p>0.05 respectively) the difference was insignificant. None from any of the two groups had PONV, pruritus, respiratory distress or need for ventilatory support.

Discussion

Measuring depth of anesthesia has become a common clinical practice, mostly due to the possibility of occurrence of awareness. Studies have shown the usefulness of BIS monitoring in prevention of awareness during anesthesia [5] and titration of propofol dose during propofol anesthesia [6]. We used BIS monitoring as a measure of an appropriate level of hypnosis in our study, maintaining the BIS score to ≤40 before intubation and 50-60 during the intraoperative period. We maintained a relatively higher BIS range (i.e. 50-60) compared to most other studies, using a lower ranges (i.e. 40-60) [5] (45-60) [7] or (40-50) [8]. However, further studies are needed to ascertain a particular BIS range for neurosurgical procedures. Butorphanol is synthetic opioids with 5-8 times more analgesic property than morphine. Butorphanol has comparable respiratory effects [9] and superior antishivering property [10] as compared to fentanyl. Agarwal et al. [11] have demonstrated that butorphanol is effective in alleviating pain due to propofol injection. This action of butorphanol can be quite useful in relieving patient’s anxiety and hemodynamic alteration arising from pain due to propofol injection before neurosurgical procedures. Previous studies have shown the usefulness of butorphanol during balanced anesthesia [12] and ability of butorphanol to provide more suitable LMA insertion condition than fentanyl [13]. In spite of all these advantages unfortunately butorphanol has not gained popularity in neurosurgical anesthesia. So we decided to use butorphanol to study the dose requirement of propofol in short intracranial procedures with and without the use of N₂O so as to know the exact required dose of propofol in neurosurgery when omission of N₂O is warranted.

In our study premedication and induction mean HR and MABP values were lower than the baseline values but (within acceptable limits) in both groups (Table 2). Previous studies have demonstrated the synergistic action of midazolam with propofol [14,15]. Following premedication, the fall in the above mentioned parameters can be attributable to the anxiolysis and sympathetic sedative effects of midazolam and butorphanol with propofol. The fall in HR and MABP was identical between two groups which show the consistency of the anxiolysis of midazolam and the sedative effects of both butorphanol and midazolam. The mean HR and MABP following intubation and during head pin application was higher in group P than group PN but the difference was insignificant. During the maintenance phase the HR at 75 and 135 mins and MABP at 105 mins following pin insertion were significantly higher in group P (propofol alone) than group PN (propofol with N₂O) [p<0.001], yet remaining within acceptable limits. However, it seemed obvious that the difference of HR, MABP between the two groups was due to the additive analgesic effect of N₂O. Butorphanol 5-8 times more potent than morphine, its use has been shown to obtund he autonomic disturbance during tracheal intubation [17,18] and the duration of action of single IV dose of butorphanol is 4 hours [19]. We observed significantly higher BIS values (p<0.01) in group P than group PN only at 45,90 and 210 minutes following pin fixation, but rest all of the values were within acceptable limits and the difference between the two groups was insignificant. As N₂O does not alter BIS values [20,21] the difference of BIS scores between the groups cannot be ascribed to the hypnotic effect of N₂O. So we believe that the difference of HR, MABP and BIS between the two groups during maintenance phase was not significantly higher.
related to N\textsubscript{2}O but could be due to other associated factors study of which was beyond the scope of our study.

Gan et al. [7] reported an overall propofol requirement of 116 µg/ kg/min, keeping BIS score of 45-60 during maintenance of anesthesia and 60-75 during the final 15 minutes of surgery. The authors reported a mean dose of 134 µg/ kg/min in their standard practice group (without BIS monitoring) of patients using midazolam sedation and alfentanil analgesia in both the groups. Previous studies have demonstrated a propofol requirement of 100-200 µg/kg/min along with N\textsubscript{2}O and an opioid analgesic in various surgeries [22,23]. In our study on intracranial surgeries using midazolam sedations and butorphanol analgesia we found an overall (79.62 ± 13.13 and 100.02 ± 20.28 µg/ kg/min) and the maintenance propofol dose (71.26 ± 11.78 and 90.82 ± 19.13 µg/kg/min) with and without the use of respectively (Table 4). Gregory et al. [24] in their study on women undergoing elective caesarean section, reported a stable hemodynamics using propofol at a dose of 100 µg/kg/min with N\textsubscript{2}O for the maintenance of anesthesia. But in our study the mean propofol dose requirement was 71.26 ± 11.78 µg/ kg/min for maintenance of anesthesia supplemented with butorphanol and N\textsubscript{2}O in neurosurgeries. Due to its unfavorable effects on cerebral hemodynamics and cerebrospinal fluid dynamics [1] and tendency to cause postoperative nausea and vomiting (PONV) [25] N\textsubscript{2}O has a controversial role in current day neurosurgical anesthesia. In our study the mean maintenance and overall dose of propofol without the use of N\textsubscript{2}O 90.82 ± 19.13 µg/kg/min and 100.02 ± 20.28 µg/kg/min respectively.

There are certain limitations in our study. First, we studied short duration neurosurgery (≤ 4 hours), because the maximum duration of action of butorphanol is 4 hours. So our results cannot be extrapolated to longer duration intracranial surgeries. Second, we used butorphanol because of the advantages of butorphanol [3,4,9,12,19,20] and problems associated during the use of newer opioids analgesics (fentanyl, remifentanil etc.) like need for frequent administration, limited availability, need for infusion system for their delivery, and their cost. Third, our study was not a blinded study. Fourth, we used alprazolam and midazolam as premedication in all of our patients which may have obscured the result. But we believe premedication is essential in neurosurgical patients as the anxiety levels are reported related to N\textsubscript{2}O but could be due to other associated factors study of which was beyond the scope of our study.

Conclusion

In short duration neurosurgery the overall and maintenance doses of propofol used along with butorphanol are 79.62 ± 13.13, 71.26 ± 11.78 µg/ kg/min respectively. Whereas, overall and maintenance doses of propofol are 100.02 ± 20.28 µg/ kg/min and 90.82 ± 19.13 µg/ kg/min respectively when N\textsubscript{2}O was omitted. These findings will help in using appropriate dose of propofol when omission of N\textsubscript{2}O is necessary during neurosurgery.

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