EFFECT OF REMIFENTANIL INFUSION ON RECOVERY IN CRANIO TOMY

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Abstract
The primary objective of anesthesia is to facilitate surgery at minimal risk to the patient and to ensure safe optimal recovery following the procedure. Early recovery from craniotomy necessitates an anesthetic technique, pharmacologically adequate to permit early awakening. This study was designed to observe the effect of different pharmacologically active drugs that permit early recovery. Thirty patients both male and female age ranges from 16 to 60 years having ASA grade I and II were randomly selected. They were equally divided into two groups. Group I received remifentanil infusion and group II received intermittent intravenous pethidine. Other drugs remained same for both group.

Group I Bolus remifentanil 1 mcg/kg followed by infusion remifentanil 0.2 mcg/kg/min. Induction by thiopental 5 mcg/kg followed by infusion of thiopental 5 mcg/kg/hr. Intubation and neuromuscular block is achieved with vecuronium. Control ventilation was maintained 65% N2O in oxygen.

In Group II, pethidine intravenously 0.5 mcg/kg before induction and 10 mcg 1/4 hourly intravenously. Induction by thiopental 5 mcg/kg followed by infusion of thiopental 3 mcg/kg/hr. Intubation and neuromuscular block is achieved with vecuronium. Control ventilation was maintained with 66% N2O in oxygen.

Anesthetic procedure was performed with monitoring of hemodynamic variables heart rate, blood pressure, SPO2, ETCO2, temperature, urine output. Data were analyzed by using unpaired t-test and Mann-Whitney-U test.

Recovery was evaluated using standardized end point. Time to spontaneous respiration, extubation, response to verbal command where significantly (P= 0.001) earlier with remifentanil than pethidine. Discharge from recovery room were earlier in group I (P= 0.015).

Introduction
The primary objective of anesthesia is to facilitate surgery at minimal risk to the patient and to ensure optimal recovery following the procedure. Recovery from anesthesia must occur predictably and safely and with minimal pain and any post operative sequels must be minimized. These objectives are achieved using balanced anesthesia with a combination of hypnotics, analgesics and neuromuscular blocking agents. Opioids are widely used as the analgesic component of balanced technique. Optimal dosing with traditional opioid is associated with adverse effect and delayed post operative recovery with risk of recurrent respiratory depression resulting from accumulation and redistribution of this drugs within the body.12,3

Prolonged recovery of the respiratory function at the end of the operation due to accumulation of opioids may delay extubation and an opioid antagonist may be needed. This is getting importance with growing practice of daycase surgery when residual effect of all anesthetics are of concern because patients are discharged home in an unmonitored environment. In neurosurgical anesthesia prolonged administration of opioid may cause prolonged recovery of respiratory function. Recurrent or delayed respiratory depression is potentially life threatening and necessitate careful post operative monitoring of patients together with ventilatory support following the use of high dose opioid anesthesia. Respiratory depression represents a particular problem in patient with renal or hepatic insufficiency who have a reduced ability to
metabolize and excrete the traditional opioids and are thus at 
increased risk of drug accumulation\textsuperscript{14}. Recurrent respiratory 
depression after bolus administration of fentanyl has been 
associated with secondary peak in plasma level. It has also 
been reported with alfentanil, sufentanil and pethidine. 
Recurrent respiratory depression may cause rapid oxygen 
desaturation and may be fatal in an unmonitored setting. 
Remifentanil hydrochloride is a potent ester metabolized 
\( \mu \)-opioid receptor agonist that has been specifically 
developed to fulfill some of the unmet needs of anesthetia. A 
prospective randomized trial has produced a short 
testing drug with rapid onset and offset of action. This allows 
the ease of titration to respond quickly to changes in 
intravenous anesthetic requirement and also permits 
optimal dosing without the risk of accumulation and 
sequential adverse effect. The rapid predictable offset of 
action of remifentanil is the result of its metabolism in the 
and tissues by nonspecific esterases.

Another important clinical benefit arising from the esterase 
metabolism of remifentanil is that recovery is predictably 
rapid across all patient groups irrespective of the duration of 
exposure. In addition, dose reduction is unnecessary in 
patients with impaired renal or hepatic function. The 
pharmacokinetic characteristics of remifentanil contrast 
markedly with those of other currently available traditional 
opioids which, when administered at optimal anesthetic dose 
may be associated with problems caused by their prolonged 
duration of action and delayed recovery resulting from 
their accumulation and redistribution within the body. This 
remifentanil offers a number of clinical advantages 
compared with traditional opioids.
Pethidine is available, less costly and conventionally used as 
analgesia for balanced anesthetic technique in intracranial 
surgery. Pethidine however is not a drug of choice in 
intracranial surgery in modern technique of anesthetia as it is 
associated with adverse event and delayed postoperative 
recovery from accumulation and redistribution of drug 
within the body\textsuperscript{15}.

Major goal of intracranial surgery is to maintain 
hemodynamic stability and normal ICP. Quick recovery 
without residual effect of anesthesia is required after 
intracranial surgery. Sustained analgesia desirable in 
intracranial surgery provided by continuous infusion of 
remifentanil cannot be achieved by intermittent intravenous 
pethidine. Pethidine currently used in our country has a low 
recovery score. Remifentanil should have even higher.

Subjects and Methods
This analytical type of observational study was carried out in 
the department of Anesthesia, Anaesthesia and Intensive care 
medicine of Bangabandhu Sheikh Mujib Medical University, 
Dhaka from July 1998 to December 1999. Thirty cases with 
different neurosurgical problem with intracranial space 
occupying lesion for craniotomy under general anesthesia 
were selected for the study. Both male and female patient 
within age group 16-60 yrs were selected. They were 
recruited and grouped randomly. The purpose of the study, 
methodology, complications, and side effects of each method 
of anesthetia were clearly explained to each of the subject 
and recruited only after they had given written consent. 
The approval of the Ethical Committee of Bangabandhu Sheikh 
Mujib Medical University, Dhaka was duly taken before 
carrying out the study.

Grouping of patients and drug treatment
Group I Remifentanil + Thiopental + piperacillin.
Group II Pethidine + Thiopental + piperacillin.

Procedure
Preoperative Management
Preanesthetic assessment was done before surgery. 
Preoperative medication that produces sedation or 
ventilatory depression was avoided in the patient with 
intracranial tumor.

Intraoperative Management
Group I patients received an injection of 
remifentanil 1 \( \mu \) g/kg/\text{IV} over 30 seconds followed by an infusion of 
remifentanil 0.2 \( \mu \) g/kg/min.
Group II patients received injection of pethidine 0.5mg/kg/IV 
followed by 10-15mg/1.5-V half hourly.

In both groups induction of anesthesia was performed by 
thiopental sodium 5mg/kg/\text{IV} in 30 seconds followed by 
infusion of thiopental 5mg/kg/hr. Patient was hyperventilated 
during the performance of induction. Patient was intubated 
with endotracheal tube and ventilated with appropriate 
circuit for controlled ventilation was maintained with 40% 
hyperventilation.

In both groups ventilation was maintained with \( \text{N}_2\text{O}+\text{O}_2 \) at 
ratio 6:4 and ventilation was adjusted to provide \( \text{ETCO}_2 
\) 20mmHg.

Intraoperative fluid was maintained with Hartman solution. 
Intravascular fluid volume depletion due to blood loss was 
corrected with the whole blood.

Intraoperatively increased intracranial pressure was treated 
with mannitol 0.5 to 0.75g/\text{min}/\text{kg}, intravenous thiopental, 
increasing the infusion dose of remifentanil, minimal 
hyperventilation, normovolemia, adequate head up position, 
free venous drainage; no compression of the jugular veins.

Incidence of bradycardia < 40/min, tachycardias > 90/min, 
hypotension MAP < 65 mmHg, hypertension > 90 mmHg 
were controlled by adjustment of remifentanil and thiopental 
infusion and by use of atropine epidural and intravenous 
fluid.

Thiopental infusion was discontinued after dual closer. 
Remifentanil infusion was discontinued at the head bandage 
and \( \text{N}_2\text{O} \) administration was also discontinued. Oxygenation 
was maintained by intermittent positive pressure ventilation 
with 100% oxygen until the return of spontaneous 
respiration. On resumption of spontaneous respiration residual 
nervomuscular block was reversed with neostigmine 0.08 
mg/kg and dose of atropine 0.02 mg per kg neostigmine. 
After resumption adequate respiration the trachea was
exhusted and time for verbal command was noted. Recovery from anesthesia was assessed using a standardized end point including time to spontaneous respiration, time to extubation, response to verbal command and eligibility for discharge from recovery room. Discharged from recovery room was assessed by Aldrete Score 10.

Statistical Analysis
All statistical analyses were performed by using SPSS for windows. Data are presented as Mean ± SD. Unpaired t-test and Mann-Whitney-U test were used to compare the difference between two groups. P<0.05 was considered as the level of significance.

Results
Demographic characteristics of patients
The age, sex and weight are presented in Table I. The median age was 35 years & range was 18-55 in years in group I and median age 30 years & range was 20-50 in years in group II. The weight (mean ± SD) were 50 ± 12 kg in group I and 54 ± 18 kg in group II. Age and weight are almost similar in two groups.

Table-I: Age sex and weight distribution of study groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>15</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/Female</td>
<td>12/3</td>
</tr>
<tr>
<td>Age, Med (range), yrs</td>
<td>31 (18-55)</td>
<td>30 (20-50)</td>
</tr>
<tr>
<td>Weight, Mean ± SD, Kg</td>
<td>50±12</td>
<td>54±18</td>
</tr>
</tbody>
</table>

Similarly time to tracheal extubation and verbal command in minute were significantly less in group I compare to group II [group I vs group II, extubation: 14 (9-20) vs 24 (15-34), (P=0.001), verbal command: 19 (15-25) vs 30 (20-55), (P=0.001)]. Discharge from recovery room was earlier in group I compared to group II, [103 (55-150) vs 155 (90-210) min, (P=0.015)].

Discussion
Anesthesia the gate way to surgery, its successful exit end with safe recovery. Recovery from anesthesia has respiratory, cardiovascular, metabolic, endocrine and neurologic consequence. Ideally patient recovery from neurosurgery should emerge rapidly from anesthesia to permit immediate assessment of the result of surgery and to provide baseline for continuing postoperative neurologic follow up.

Recovery was assessed using standardized end point including time to spontaneous respiration, extubation, response to verbal command and eligibility for discharge from recovery room.

Time to spontaneous respiration earlier in remifentanil than pethidine. Return of respiration was smooth than pethidine. Time to adequate spontaneous respiratory rate followed by extubation was earlier with remifentanil. Response to verbal command was also earlier with remifentanil. Psychomotor and psychometric function better with remifentanil than pethidine. Quality and speed of recovery was better with remifentanil. Recovery with remifentanil statistically significant than pethidine.

In a study done by Cartwright et al., 1997 remifentanil was compared with alfentanil as part of balanced anesthesia with 0.8% isoflurane in both groups. Remifentanil patients response significantly with better recovery of psychomotor and psychometric function. Recovery was earlier and better with remifentanil. Present study used thiopental. Thiopental produce dose dependent reduction in CBF\(^\text{以外}\), CMRho2 and IPC. Thiopental attenuates cerebral vasodilation produced by N\(_2\)O.

A comparison study of elective craniotomy between remifentanil and alfentanil done by Sneyd et al.\(^1\). Bolus injection of remifentanil 1µg/kg followed by infusion of remifentanil 0.5µg/kg/min in one group. Bolus followed by infusion of alfentanil in other group. Alfentanil followed by remifentanil in another group. Propofol was used for induction & maintenance. Lungs were ventilated with 66% N\(_2\)O in O\(_2\). Median times to tracheal extubation and obey commands were similar in all groups. The process of recovery was qualitatively different with remifentanil group with patient emerging suddenly with near synchronous return of respiration, tracheal extubation & responses to command.

Table-II: Recovery time from anesthesia following intravenous administration of study II anesthesia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (median (range))</th>
<th>Group II (median (range))</th>
<th>Group I vs Group II p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to spontaneous respiratory rate</td>
<td>9 (5-15)</td>
<td>15 (12-20)</td>
<td>0.001***</td>
</tr>
<tr>
<td>Time to tracheal extubation</td>
<td>14 (9-20)</td>
<td>24 (15-34)</td>
<td>0.001***</td>
</tr>
<tr>
<td>Time to response to verbal command</td>
<td>10 (15-25)</td>
<td>30 (20-65)</td>
<td>0.001***</td>
</tr>
<tr>
<td>Discharge from recovery room</td>
<td>9 (5-13-50)</td>
<td>18 (90-21)</td>
<td>0.015***</td>
</tr>
</tbody>
</table>

Data are presented as Median (range). Mann-Whitney-U test was one test of the test of significance.

***p<0.001

Time to spontaneous respiratory rate in group I was median (range) 9 (5 - 15) min and 18 (12-25) min in group II. Recovery time was significantly (P=0.001) less than group II.

Conclusion
Early recovery a major goal of intracranial surgery anesthesia is achieved by remifentanil. Though costly its unique clinical advantage make it superior to pethidine.
Reference: