SECTION 1: ANAESTHESIA

COMPARISON OF PROPOFOL WITH THIOPENTONE SODIUM AS INDUCTION AGENT IN DAY-CASE SHORT GYNAECOLOGICAL PROCEDURES

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ABSTRACT

Thiopentone has been the gold standard as an induction agent. In the recent past, a number of new agents were tried, including methohexitone, etomidate and propofol. Out of these only propofol could stand the test of the time, and is widely used throughout the world. We designed a study to compare thiopentone and propofol as induction agents. Haemodynamic effects of both drugs during induction as well as duration of apnoea and other subjective criteria were studied. Recovery profile, including quality of recovery, incidence of side-effects and the patient preference were also studied. There was a significantly increased incidence of involuntary movements in propofol group as compared to thiopentone group, Group-I (19 vs 13). The onset of effect was 25.28 (SD 27.32) in Group-I, and 21.12 (SD 27.92) in Group-II, (propofol group). The fall in mean blood pressure was not significantly different in both groups, maximum fall noticed after five minutes. On recovery, the incidence of post operative nausea/vomiting was less with propofol, (four times higher in thiopentone group) and the recovery was faster in this group (11.8±5.4 vs 6.7 ±3.0 min). The quality of recovery was better in this group, and more patients felt euphoria and satisfaction with propofol. We conclude that propofol is a better induction agent, when rapid recovery is desired in day case short procedures, but it is expensive and associated with more involuntary movements as compared to thiopentone.

Key Words: propofol, thiopentone, induction, induction agent, haemodynamic effects, post-operative nausea/vomiting

INTRODUCTION

Intravenous agents may be defined as "the drug which will introduce loss of consciousness in one arm brain circulation time when given in appropriate dosage". For a drug to produce rapid onset of unconsciousness, it must penetrate blood brain barrier rapidly and produce high local concentrations within the brain, so the drugs which have low degree of ionization and are lipid soluble, cross blood brain barrier rapidly and are therefore, effective induction agents.

Thiopentone was synthesized in 1932 by Ernest Henry Volwiler and Donalee Tarben and introduced into clinical practice by Lundy of the Mayo clinic on 18th June, 1934 and by waters of Madison on 3rd March, 1934 and since long has been universally accepted as inducing intravenous anaesthetic agents. Thiopentone is a barbiturate derived from Barbituric acid, is lipid soluble and has low degree of ionization. It crosses the blood brain barrier rapidly and produces loss of consciousness within one arm brain circulation time.

Thiopentone is sodium ethyl (1-methyl butyl) thiobarbiturate. It is the sulphur analogue of pentobarbiturate. It is a yellow amorphous powder with odour resembling H2S. It is soluble in water and alcohol and forms a 2.5 or5% solution in distilled water of pH 10.5 which is highly alkaline as compared to blood with pH of 7.4.

Due to high pH and alkalinity, the solution causes pain, redness and swelling, haematoma formation and rarely ulceration if extravasation occurs on giving it intravenously.

Although thiopentone is a very satisfactory inducing intravenous anaesthetic agent, but as mentioned above, many problems are faced by its use and it is contraindicated in certain situations, so new drugs have been tried and evaluated as inducing agents e.g. Hydroxydine 1955; Propanidid 1956; Althesin 1971; Eketamine 1965; and Propofol 1977.

Propofol was first introduced in 1977 and since then extensive clinical experience in a wide variety of patient types and surgical procedures has demonstrated its effectiveness as a general anaesthetic.
Propofol is extensively distributed and rapidly metabolized to inactive metabolites. These features form the basis of a pharmacokinetic profile which makes propofol suitable for administration by continuous infusion. In addition this profile enables easy adjustment of depth of anaesthesia, and facilitates a swift, clear headed recovery. It is 2,6 diisopropylphenol having a molecular weight of 178 and is available as a sterile oil-in-water emulsion, each vial contains 1% W/V (10mg/ml) of propofol.

When used in anaesthetic doses, few excitatory effects are seen at induction. It produces greater degree of reflex depression than thiopentone. Recovery from anaesthesia is rapid as cumulative effects of propofol are minimal and insignificant when compared with thiopentone. Generally there is fall in mean arterial blood pressure. Reduction in cardiac output is due to direct vencodilator effect causing a decrease in pre-load. Over dosage of propofol produces apnoea and dose related hypotension. Neither histamine release nor anaphylactoid responses were seen after its administration.

Day case surgery has taken its roots and established itself as an accepted routine for short surgical procedures. It has many advantages as regards to convenience for patient's reduced costs, reduced bed occupancy as well as convenience to the relatives of the patient.

Short surgical procedures, such as small excisions, incision & drainage, reduction of simple fractures, change of dressings, uncomplicated hernia repairs, anal dilatation etc. can safely be performed as day-case surgery. Gynaecology & obstetrics is no exception to this rule, and diagnostic as well as therapeutic D&C can conveniently be undertaken on day-case basis.

Day-case anaesthesia has some peculiarities as compared to that for admitted cases. Over dosage must be scrupulously avoided, post-operative nausea, vomiting, vertigo, headache, bronchospasm and cardiovascular instability avoided at all cost. The patient's leaving for home must be clear-headed and their responses intact to guard against any untoward effects which may threaten the safety of the patient, on their way and after reaching home. Propofol has clear edge over thiopentone in this regard. Our study compared various parameters during induction as well as recovery, using both drugs.

MATERIALS AND METHODS:

Fifty patients with the following criteria were selected for this study in Gynaecology and Obstetrics Department of CMH Sialkot during 1995-96. All of these patients were scheduled to undergo Dilatation and Curettage (D&C), for various indications.

1. Age: 20-40 years
2. Sex: Females
3. ASA Patient Status I & II

Then these patients were referred for pre-anaesthesia assessment with the following investigations.

1. Urine RE
2. Blood CP
3. X-Ray chest PA View
4. ECG
5. Blood Sugar Fasting and Random

Patients were assessed in a systematic way.

History: A proper and detailed history pertaining to the following was taken:

1. Cardiovascular system including pulse rate changes, h/o high blood pressure, dyspnea after walking or climbing stairs, episodes of angina and myocardial infarction and management if any.
2. Respiratory system including cough, sputum, bronchial asthma etc. and treatment if any.
3. H/O any neurosurgical disease, liver or renal disease, diabetes mellitus, any drug intake and its duration as well as any drug allergy was also sought.

General Physical Examination and systemic examination, with particular emphasis on Respiratory System, CVS, Hepatic and renal system was carried out An estimate of pre-operative blood loss and a predication of blood transfusion were carried out. Patients were also assessed for intubation difficulty, and all patients with probable airway problems were excluded from the study.

Exclusion Criteria: Patients with history of renal or hepatic disease and those taking medications known to effect intravenous anaesthetic agents were excluded. No case of difficult intubation was included in this study. Patients with ASA status III & IV were also excluded. All procedures continuing beyond a duration of half an hour were judged to effect the outcome at the time of recovery, so such patients were excluded from the study.
Then these patients were divided into two groups:
each consisting of 24 patients.

a. **GROUP I**: Induced with thiopentone. No 
premedication was allowed.

b. **GROUP II**: Induced with propofol. Again no 
premedication was allowed.

4. The criteria for induction was sleep induction and 
loss of consciousness i.e. loss of verbal command, loss 
of eyelash and corneal reflexes. Anaesthesia was 
maintained with nitrous oxide in oxygen and 1% 
Halothane. Patients were allowed to breathe 
spontaneously. However, in some patients with prolonged 
apnoea IPPV had to be used initially. The cuffs of both 
manual sphygmomanometer and non-invasive 
intermittent BP monitor applied; systolic, diastolic and 
mean blood pressure and pulse rate were monitored 
perioperatively. Arterial oxygen saturation SpO2) was 
monitored with pulse oximeter Heart rate, systolic, 
diastolic and mean arterial blood pressure were measured 
and recorded at 1 minute before induction, 2 minutes 
after induction and then at fixed intervals. Near the end 
of operation N2O and halothane were turned off, and 
100% O2 was administered.

5. In each group, the following study was done:
   a. Induction time.
   b. Duration of apnoea and other respiratory 
      problems on induction.
   c. Haemodynamic changes i.e. systolic, 
      diastolic, mean blood pressure and pulse changes on 
      induction and during maintenance of anaesthesia
   d. Quality of anaesthesia.
   e. Recovery characteristics e.g. recovery time, 
      quality of recovery.
   f. Any complications.
   g. Cost effectiveness.

**RESULTS:**

The distribution of patients in both groups is shown 
in Fig. 1. The patients in Group-I belonged to 
comparatively a lower socioeconomic group. This fact 
is proved by the weight distribution graph, as 11 patients 
fell within first two classes, as compared to 8 in the 
second group. Secondly, the number of patients over 
60 Kg was merely 4 in the first group as compared to 10 
in the second group. It was observed that the onset 
of effect was significantly increased in the second group – 
(Mean 26.28 seconds, Standard Deviation 15.13 
Seconds). In this group number of patients with onset 
of effect of 30 or more than 30 seconds was 11, as 
compared to 5 in the first group. Similarly the number of 
patients with a delayed onset of more than 40 sec was 
four in group-II as compared to one in group-I. The mean 
duration of onset of effect in group-I was 18.21 sec with 
Standard Deviation of 13.98.

Fig 2 shows a comparison between thiopentone and 
propofol regarding onset of effect.

The quality of induction in both groups is shown in 
Table 2. The incidence of complications during this phase 
was similar, with the exception of bronchospasm, which 
ocurred with the use of thiopentone. Apnoea was the 
main complication observed in both groups (Fig. 3). The 
mean duration of apnoea in Group-I was 25.28 sec (SD 
27.32) and in Group-II, it was 21.12 sec (SD 27.92) Again, 
the number of patients with duration of more than 30, 50 
and 60 sec was 8, 6 and 2 respectively. The equivalent 
number in Group-II was 6.2 and 1.
The comparative effects of both drugs on pulse are shown in Fig. 4. The number of patients exhibiting an increase in pulse rate on induction was 17 in Group-I and 7 in Group-II. None of the patients showed bradycardia. There was a generalized trend of increase in pulse rate with thiopentone as compared to propofol, which showed a decrease. This change in heart rate is consistent with the duration of apnoea, so observed with both.

The comparative effect on BP by both of the drugs is shown in Fig. 5(a) & 5(b). It can be appreciated that thiopentone caused a slight fall in systolic BP, but a slight increase in diastolic BP. The effects were more pronounced after 6 minutes. On the other hand propofol caused a fall in both systolic as well as diastolic BP. The maximum effects again were seen after 5 minutes.

The mean recovery times are shown in Fig. 6(a) & 6(b). The recovery was significantly delayed in thiopentone group with a mean of 11.8 min (SD 5.4). The mean recovery time with propofol was 6.7 min (SD 3.0). Quality of recovery is compared in Table 1. The incidence of shivering and muscular movements was one in Group-I, but none in Group-II, euphoria was observed in 8 patients in Group-II, and 2 patients in Group-I. Thus the quality of recovery was definitely better with propofol.

The cost-effectiveness of both drugs is shown in Table 2. On per patient basis, propofol may seem to be more expensive, but on a larger scale, when seen in terms of hospital stay with additional expenditure it can be concluded that propofol is a better drug in this regard too.
DISCUSSION:

Thiopentone has been widely used as an induction agent. Vast experience of its clinical use has led us to a thorough understanding of its pharmacokinetics, pharmacodynamics and the different settings of its therapeutic role in the field of anaesthesia.

The classical signs and stages of ether anaesthesia are not seen with thiopentone because induction is rapid. The clinical level of anaesthesia produced by thiopentone is related to the intensity of surgical stimulation as well as degree of cerebral depression. Thiopentone usually produces short-lived surgical anaesthesia within 1 or 2 minutes. The mean onset of effect in my study was 18.21 sec (±13.98). The number of patients with duration of more than 30 sec was five and in only one patient the onset was delayed for more than one minute. Six out of 8 patients with an onset time of more than the mean were over 50 kg in weight.

The onset was rapid in dehydrated and under weight patients due to low volume of distribution, as it is in low serum albumin (e.g. severe liver disease, malnutrition). Higher brain and higher concentrations will be achieved for a given doses. Another fact proved by this study is that cumulative effects probably do occur after thiopentone use and the dose required to maintain unconsciousness becomes progressively less. The mean dose of succeeding boluses reduced from 257.2 mg + 42.5 to 81.6 mg + 46.8 and then to 68.8 mg + 28.9. As the surgical procedure in most of the cases lasted for only a few minutes the third bolus was needed to be given to only 4 out of 25 patients.

In contrast, the onset of action in case of propofol was slightly delayed, the mean being 26.28 + 15.13 minutes. Eleven out of 15 patients took more than 30 sec. In this group, Propofol is highly lipophilic and distributes rapidly and extensively from blood into brain and tissues. The initial dilution volume greatly exceeds blood volume. The obesity effects of rate of clearance, being greater in patients whose body weight exceeds the idea1. The use of volatile anesthetics in conjunction with I.V. anesthetics results in a reduction of volume of distribution of propofol both in the central compartment and during elimination phase22. This effect has not been considered here as maintenance of anaesthesia was supplemented in both groups with 1% halothane, so equivalent effect in either group is assumed. Without halothane, movements in response to surgery have been reported23.

The duration of apnoea was identical in both groups, being about 20% greater with thiopentone. The incidence and duration of apnoea varies but tends to be closely related. It can be exacerbated by ventilating with 100% oxygen24 and pre-treatment with opioids25. In a study by Goodman et al, apnoea occurred in 11 out of 14 patients26. Thiopentone and propofol both depressed minute volume.

In prolonged apnoea, ventilation can easily be maintained with manually compressing the bag, and does not present the anaesthetist with any difficulties.

Propofol is known to produce pain on injection site, if given in small veins and especially in veins on the dorsum of the hand. The reported incidence varies form 10% to 15%27.

In my study, I used 1.5 ml of 2% lignocaine per 20ml of propofol. So the pain was complained by only 2 patients in either group. The apparent lack of effect by lignocaine in these patients was probably due to too small an induction dose of propofol used, which resulted in proportionate reduction in dose of lignocaine.

Complications like haemangitis, skin rash, hiccups and cough was not observed in any of the patients in both drug groups. Hiccups and cough have been reported to occur with the use of propofol, the incidence of cough being 1.9%. Laryngeal reflexes are more effective after induction with thiopentone than with equivalent doses of propofol28, and in my study one patient developed bronchospasm in thiopental group. However, it was easily overcome by use of salbutamol inhaler. The minimum use of pharyngeal airway was an important factor in low incidence of laryngospasm/bronchospasm in my patients29.

Although the incidence of involuntary movements was 50% higher in thiopentone group, (Table 9-3), this occurred probably due to early start of the surgical procedure in lightly anaesthetized patients. The muscle spasm was observed in five patients (20%) in propofol group, compared with 2 (8%) in thiopentone group. This is consistent with no significant direct effect by thiopentone on the neuromuscular junction. Mackenzie and Grant reported a 20% incidence of movement with propofol30. In my study the figures are almost 50% for propofol and 76% for thiopentone.

Thiopentone is notorious for producing hypotension which is probably due to venodilation. It is more marked in hypovolaemic or hypertensive patients. Direct cardiac depression occurs with higher doses of thiopentone31. My study concludes that at low dose there is minimal decrease in systolic blood pressure, with slight increase in diastolic pressure. Maximum fall was observed after five minutes and this effect was nullified after termination.
of anaesthesia as the patient regained her reflexes. After fifteen minutes the blood pressure was almost equal to the pre-induction level.

A bolus administration of propofol is accompanied by a decrease in systolic, diastolic and mean arterial blood pressure. There is reduction in systemic vasculature resistance and cardiac output generally decrease by less than 20%\(^3\). I observed a fall of about 20% in mean diastolic pressure and a fall of about 14% in mean systolic pressure. Direct vasodilator and negative inotropic may be involved in production of hypotension, but the mechanism is not clear. The decrease was pronounced in patients who where hypertensive prior to induction. A fall of 30% was observed in a patient with pre-induction systolic blood pressure of 157 mm Hg.

This group was also different from the thiopentone group in that the mean systolic and diastolic pressure remained low even after termination of the anaesthesia for a variable length of time.

Propofol lacks vagolytic activity and can cause bradycardia, occasionally profound\(^3\). The effect of thiopentone is variable. The fall in cardiac output and blood pressure is usually compensated for by increased sympathetic activity mediated by baroreceptor reflexes. I observed development of tachycardia with thiopentone, an effect that was offset after about 12.5 minutes. The propofol group had general tendency of fall in heart rate with a mean fall of 19% after fifteen minutes as compared to mean fall of 8% in thiopentone group. Thus, the haemodynamic effects of both drugs can be judged to be comparable, with only minor difference in mean values of different parameters.

However, propofol has established its superiority in the recovery phase. Recovery with propofol is significantly faster\(^3\). It has been reported by Jessop et al and Mackenzie and Grant in two different studies that recovery was quicker after propofol with regard to clear headness and alertness, than with thiopentone\(^5\)-\(^6\). My study confirms this and shows that the mean time from termination of anaesthesia to raising head was 11.8 + 5.4 minutes with thiopentone, and 6.7 = 3.0 minutes with propofol. Thus propofol had 43% shorter recovery time. Also quality of recovery was much better with propofol (Table 1) euphoria occurred in eight patients with propofol as compared to two patients in thiopentone group. Similarly incidence of shivering was 4% in thiopentone group, nausea / vomiting occurred in 18% of patients in this group. None of the patients in propofol group exhibited shivering or muscular movements during recovery; and only one patient vomited (4%). The patients were more clear-headed, cheerful and eager to go to home. Twenty two patients were discharged just after one hour (88%) and none was retained beyond two hours.

In thiopentone group, only nine patients could be discharged after one hour. Eleven patients (44%) had to be retained beyond two hours and four out of these (16%) had to be admitted for an overnight stay.

Although studies regarding cost effectiveness of thiopentone and propofol in day-case patients in our country are not generally available, the cost of hospital admission per bed in a military hospital has been calculated to be Rs. 500/- per day\(^3\). The comparative figures for both drugs are given in Table 2. It can be seen that propofol is 560% costly (cost of one ampoule of propofol being Rs. 240/-) than thiopentone (cost Rs. 36/- per ampoule), other things being equal. But the

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<th>QUALITY OF RECOVERY AND FOLLOW-UP</th>
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<td>Cost With Over-Night Hospital Admission(^*)</td>
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patients who have to be admitted show a 123% increase in cost per patient than a patient who received propofol and did not need to be admitted. The incidence of hospital admission in case of thiopentone was 16% as compared to zero with propofol, as mentioned earlier. The anxiety of staying at hospital away from the family, the risk of acquiring hospital infections and increased loss of working hours per patient dictate the routine use of propofol as induction agent in at least day-case (ambulatory) surgery.

CONCLUSION

My study concludes that thiopentone remains the mainstay of induction agents with a few exceptions. Its use is absolutely contra-indicated in porphyria. A few other complications such as the risk of intra-arterial injection and its consequences, as well as its effects on haemodynamics notwithstanding, its use in clinical anaesthesia will continue in the days to come.

Newer agents e.g. propofol have some benefits over thiopentone. Propofol is especially useful as an induction agent for day-case (ambulatory) anaesthesia as the patients' recover comparatively clear-headedly and are fit to leave for home sooner. It can safely be used in patients with history of bronchial asthma.

The incidence of some of the complications e.g. nausea/vomiting, shivering and bronchospasm/laryngospasm is comparatively higher with thiopentone but the use of propofol is fraught with a higher incidence of muscular spasm and involuntary movements during induction.

Although the costs of anaesthesia with thiopentone are comparatively low than propofol but if the costs of hospital admission, as well as the inconvenience to the patient and his family and the lost working hours are taken into account, then it may be concluded that propofol is the drug of choice for day-case (ambulatory) anaesthesia.

REFERENCES:

4. Lundy JS, Tovell RM, North West Med, 1935; 33; 308
10. Mackenzie N, Grant IS, Propofol For Intravenous Sedation, Anaesthesia 1987; 42:3-6
12. Richardson J, Propofol infusion for Coronary Artery Bypass Surgery in a patient suspected Malignant Hyperpyrexia, Anaesthesia, 1987; 42:1125


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