Time course of psychomotor, cognitive and ambulatory recovery after Propofol day case Anesthesia: A randomized double blind study.

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Abstract

Aim: A double blinded randomized study was designed to evaluate the time course of psychomotor, cognitive and ambulatory recovery after Propofol anesthesia and compare it to Thiopentone as induction agents. Methods: 100 patients undergoing short gynecologic procedures received either Propofol or Thiopentone for induction and nitrous oxide, oxygen and or halothane for maintenance of anesthesia. Immediate recovery (time from nitrous oxide shut off, response to pain, spontaneous eye opening, response to commands and three point orientation noted). Battery of 7 bed side psychomotor tests (Mail box, Manual dexterity, aiming, DSST, Trieger dot, pictorial recall, auditory motor coordination were recorded preoperatively and at 15 min, 30 min, 1hr, 2hr, 3hr, 4 hr postoperatively. Results: Emergence, ambulation and psychomotor recovery was significantly faster and consistent in Propofol group compared to Thiopentone. Thiopentone group was impaired even at 4 hrs, particularly at Trieger dot test and manual dexterity. Propofol group remained impaired for 1hr at mail box test, manual dexterity test and DSST and 2 hrs at Trieger dot, aiming and auditory motor coordination.

ABBREVIATIONS

DSST - Digit symbol substitution test.

MAC – Minimum alveolar concentration.

INTRODUCTION

Propofol is a good drug for ambulatory anesthesia because of its unique pharmacodynamic and pharmacokinetics. We decided to study and compare the efficacy of ‘Propofol’ an intravenous agent with another intravenous agent ‘Thiopentone’, with a detailed monitoring of early and intermediate recovery stressing on psychomotor and cognitive effects and ambulatory recovery from anesthesia, particularly the time course of recovery events. We also evaluated the sensitivity of psychomotor tests used.

METHODS

An institutional ethics committee approval was taken prior to beginning of clinical trial. An informed, written consent was obtained from patients volunteering for study prior to their initiation in it. An anesthesiologist performed a history and thorough physical examination to enroll suitability of subjects for study. 100 female patients of 18-50 years, ASA grade I /II, undergoing elective Obstetric and Gynecological D&C were enrolled. Patients with clinically significant cardiovascular, respiratory, hepatic, renal, allergic history, psychological and neurological disorders were excluded. Patients were randomly allocated to one of the two groups. Group A had induction with Thiopentone 5 mgkg if followed by nitrous oxide 60-65%, oxygen 30-35%, halothane 0.5 % MAC if required and intermittent bolus of 25 mg Thiopentone. Group B had induction with Propofol 2mgkg followed by nitrous oxide60-65%, oxygen30-35% and intermittent bolus of 10 mg Propofol. Anesthesiologist observing the preoperative and postoperative psychomotor tests remained blinded to type of anesthesia till the end of trial. Anesthesiologist administering anesthesia remained blinded to recovery recordings. All subjects were asked to refrain from alcohol, sedatives and tobacco 24 hr prior to surgery. They were also told not to drive a car, operate machinery for 24 hr after anesthesia and also asked to be escorted home.

Day prior to surgery the patients were made accustomed to 7 psychomotor tests used in this study. After three attempts, a final attempt was taken as baseline. The tests were
performed in sitting position with the dominant hand after baseline pulse and blood pressure were recorded. Injection glycopyrrolate 0.004mgkg\(^{-1}\) was administered intramuscularly 30 minutes before induction. Monitoring included continuous ECG, pulse oximeter, non-invasive blood pressure. 20 G, intravenous canula was secured on the non dominant hand. An infusion of dextrose with normal saline was started prior to induction. Analgesic Tramadol 50 mg was given intravenously. Patients were induced with Thiopentone 5mgkg\(^{-1}\) or Propofol 2mgkg\(^{-1}\) intravenously slowly over 30 seconds till loss of eyelash and eyeballs were centrally fixed. Induction was carefully observed for occurrence of any apnea, cough, twitching, hiccup or involuntary movements. Anesthesia was maintained with nitrous oxide 60-65%, oxygen30-35% and intermittent boluses of either Thiopentone 25 mg or Propofol 10 mg as required maintaining the surgical plane and hemodynamics within 20% of baseline. Halothane MAC 0.5% was also administered in Thiopentone group of patients as required. The patients breathed spontaneously via Magill circuit. Every five minutes pulse and blood pressure were recorded. The time of induction and time of each bolus drug administered were recorded. The total dose of drug given and time of end of surgery and nitrous shut off were noted. Time at which patient responded to painful stimuli, opened eyes spontaneously, responded to verbal commands and recalled address was noted in order of occurrence. When a patient responded to verbal commands and had stable hemodynamics was transferred to recovery room. In the recovery room each patient was assisted to sit up every 5 minutes. After a patient could sit unaided, was asked him/her to stand with support and subsequently without support by the blinded observer anesthesiologist. Once a patient stood without support, he/she was assisted to walk with and without support. Times at which sitting and standing with and without support occurred were recorded. Walking with and without swaying to one side and climbing stairs up and down a 2 step wooden block of stairs was recorded.

Patients were subjected to psychomotor tests first at 15 minutes from nitrous oxide shut off time and then at 30 minutes, 1 hr, 2 hr, 3hr and 4 hr respectively. A battery of 7 tests included were Mail box test, Manual dexterity test, Aiming, Trieger dot test, DSST (Digit symbol substitution test), Pictorial recall memory test and Auditory motor coordination test.

Mail box test (modified version of peg board test) measured dexterity of gross and fine movements (manipulative skills) requiring eye/hand coordination and Visuo spatial functioning. Patient was asked to fit in 24 different geometric shapes in their respective slots and was scored by the number of correctly placed shapes in a predetermined time measured by hour glass.

Manual dexterity test assessed hand to eye coordination involving both fine and gross motor movements and visual functions with concentration. Patients were asked to guide a 4.5 cm diameter loop with 11 cm handle along a twisted length of wire with 4 curves in semicircles of 4.0 cm diameter each without touching it. The dimensions of loop and curves were standardized after a series of pilot readings taken prior to study. Scoring was done by number of times wire was touched by loop.

Aiming test was specifically designed to measure speed in addition to Visuo-motor coordination. In 90 seconds patients had to mark a dot in center of 300 circles of 2.5mm radius drawn on 1 cm graph paper. Numbers of circles centered in 90 seconds were recorded.

Trieger dot test measured hand eye coordination and was a simple paper pencil test requiring patients to connect 21 dots in the form of letter S with a micro tip pen. Scoring was done by calculating number of dots missed.

DSST (Digit symbol substitution test) measured recoding skills and recognition of sensory (visual) information, mental concentration, fine muscular coordination and ability to alter eye fixation. In DSST patients were given 90 seconds to replace 30 randomly arranged digits with appropriate symbols located in a legend at the top of the page. To avoid practice factor obscuring results in this test particularly, new set of arrangement of 30 digits were given to patient.

Pictorial memory recall test was designed to measure recent past memory (short term memory) by asking patient to memorize and recall in ten minutes, pictures of 3 animal cards among 15 others. Patients received a clue if they failed to recall anyone of the cards. Scoring was in the form of simple yes if recalled correctly and or no if they failed to do so.

Auditory motor coordination test measured auditory perception, attention and simple reaction time as had motor component in it. Patients were asked to hear different sets of bell rings comprising of 1, 2 or 3 maximum 4 rings and
asked to indicate number of rings heard by raising appropriate number of fingers. The numbers of correctly heard rings were recorded.

Post operative adverse effects like headache, confusion, nausea, vomiting, giddiness and pain at injection site were recorded. Patient experience of anesthesia was recorded as a grade excellent, good, fair and poor respectively.

**STATISTICS**

Distribution of patients with respect to age, weight, duration of surgery and duration of anesthesia was compared with unpaired ‘T’ test. Incidence of adverse events at induction and post operative complications were studied and compared between the two groups using chi X² analysis. All parameters of early recovery and psychomotor recovery tests were recorded as mean ±S.D (standard deviation). To assess impairment within each group as compared to baseline students paired ‘T’ test was used. Impairment with respect to baseline of one group was compared to impairment with respect to baseline of other group using independent samples unpaired ‘t’ test. P< 0.05 was considered as significant. Finally to assess patient overall experience of anesthesia in the two groups was tested by Pearson chi squared test.

**RESULTS**

There was no statistically significant difference between the two groups with respect to age, weight, duration of Anesthesia and surgery.

Early recovery (awakening) from anesthesia was significantly faster in Propofol than Thiopentone group. Patients receiving Propofol anesthesia responded to pain in 2 minutes and were able to obey verbal commands as early as 5 minutes. Thiopentone group took longer 6 minutes to open eyes and 13 minutes to obey commands from nitrous oxide shut off time. Propofol group recalled address in 6 minutes which took 16 minutes for Thiopentone group (Chart 1).

Concerning the variables of home readiness, including patient’s ability to sit, stand, walk, climb without support, dress themselves, tolerate oral fluids and be judged fit for discharge, there was a significant difference in the two groups. Propofol group was able to sit with minimal support as early as 15 minutes and was eligible to perform first round of psychomotor tests offered at 15 minutes as compared to Thiopentone group who took 38 minutes to sit with support. Standing with support and without support for Propofol was possible at 38 and 50 minutes respectively (chart2).

Patients receiving Propofol clearly walked with support, with mild swaying and without support significantly (P < 0.001) faster than Thiopentone group. Patients in Propofol group could climb 2 step blocks of stairs both up and down in 88 minutes.

**PSYCHOMOTOR RECOVERY**

Psychomotor recovery was significantly faster and consistent with Propofol anesthesia as compared to Thiopentone in all 7 psychomotor tests. Thiopentone group remained impaired at 4 hrs (p< 0.01) as compared to Propofol group which recovered to baseline by 1 hr at Mail box, manual dexterity and auditory motor coordination. Impairment in Propofol group lasted for 2 hrs at aiming, DSST and Trieger dot test. Impairment at every time interval in Propofol group was significantly lower than in Thiopentone group.

The performance at psychomotor tests is detailed in the charts (3, 4, 5, 6, 7, and 8) below.
DISCUSSION

The very idea of faster recovery, early ambulation has attracted patients especially children and elderly, who prefer less separation from their familiar home environment.

This study clearly demonstrates that, in short duration surgeries, Post operative recovery with respect to early recovery (awakening), intermediate recovery (psychomotor and cognitive recovery) and ambulation “home readiness” is significantly (P<0.001) faster and consistent after Propofol anesthesia. Propofol has been compared to inhalational agents like Desflurane in out patient surgery, reporting that Desflurane has more rapid emergence and is cost effective than Propofol, but has complications like nausea and vomiting affecting discharge, and of course patient discomfort (1,5). Inhalational agent with a low blood gas partition coefficient, Sevoflurane was used as a maintenance agent in comparison to Propofol and showed rapid emergence from anesthesia; but had a higher incidence of nausea vomiting, so did not result in any difference in discharge time from hospital (6). In agreement with previous studies (7-16), post operative recovery observed in this study was faster and consistent with Propofol, compared to Thiopentone. However, the magnitude of advantage of Propofol over Thiopentone was small and less elaborated in most of the previous studies than present study. Despite the theoretical advantage of shorter distribution half time and ten times rapid metabolic clearance of Propofol over that of Thiopentone (16-19), it was not elaborately highlighted in clinical findings in all previous studies. One explanation for this could be that in most of these studies, a combination of drugs such as sedatives and muscle relaxants were used, therefore residual effects of drugs and their interaction with the induction agents may have led to delay in the onset of recovery. In our study we avoided use of sedatives and muscle relaxants. Halothane was used in Thiopentone group to limit the dose of maintenance of Thiopentone and to avoid any prolonged respiratory and cardiovascular depression due to Thiopentone which could have obscured recovery readings. We also restricted the maximum halothane use to 0.5 % keeping in mind its dose dependent uterine suppression (20) in obstetric D&C. Propofol group did not require halothane for maintenance of anesthesia which is an advantage of Propofol attributed to its faster clearance even more so after bolus administration (19). However, some studies have even found marginal or no difference in the two anesthetics with respect to their induction and effects on psychomotor recovery (21-23). There were some limitations related to subject bias, confounding variables, and even investigator related bias in one such study where subjects involved were only military personal, lack of blinded study methods and use of a single psychomotor test to judge recovery. Our study was a carefully designed randomized double blinded, prospective study to give valid comparison of the two anesthetics. There was a team of 3 Anesthesiologists who remained consistent throughout this study avoiding any investigator related bias. The observer
anesthesiologist monitored and recorded preoperative and postoperative psychomotor tests was blinded to drug of anesthesia and the other two anesthesiologist administered anesthesia remained blinded to recovery results till end of the trial. Some of the previous studies did not keep consistency with duration of anesthesia and duration of surgery which might prolong recovery. Our study groups were comparable in age, weight, duration of surgery and anesthesia and had similar distribution of obstetric and gynecological D&C procedures. We also tried to maintain a consistent plane of surgical anesthesia, though we did not monitor the depth of anesthesia which is one of the limitations of this study. There was yet another study by Kern et al in 1998 in which Propofol had a rapid early recovery than Thiopentone, but intermediate and late recovery in the two groups were similar (26). However this study used a combination of subjective and objective end points as results and also had a smaller number of subjects in the study as opposed to our study comprised of 100 patients and used only objectively assessed psychomotor tests and scoring system. Tramadol and Diclofenac rectal suppository were used for analgesia to avoid any depressant effects on recovery.

Awakening from anesthesia was time taken to obey simple verbal commands from nitrous oxide switch off time. In all earlier studies recovery time was calculated from end of procedure and not from time of stoppage of last anesthetic agent. In 1988 Sear et al (23) have reported that recovery time was significantly less in Propofol (9.7 – 14.8 min) as compared to Thiopentone (14.2-22.2 min). In Sanders study awakening in Propofol was at (6.7 ± 3.4 min) compared to Thiopentone (21.4 ± 9.1). In present study awakening was seen as early as (4.7±1.47 min) in Propofol group and (13.6 ± 4.5 min) in Thiopentone group. Propofol group could recall address at 5 min as opposed to Thiopentone group took 16 min for the same.

Assessment of ambulation as recorded in this study, was the time at which patient could sit for the first time with support at 15min and without support at 26min, stand with support at 38 min and without support at 50 min and walk with support at 61 min, mild swaying 72 min, and without support 84 min in Propofol group. Thiopentone group sat with support at 39 min, sat without support at 45 min, stood with support at 65 min, stood without support at 85 min, walked with support at 107 min, walked with mild sway at 125 min and walked without support at 141 min. All the parameters recorded were faster than Sander’s study, which reported Propofol group could sit at 43 min and stand by 1 hr as compared to Thiopentone group sat at 80 min and stood at 2 hrs. One explanation to this discrepancy in readings in both studies could be due to a smaller number of subjects in previous study and recovery recordings done at fixed time intervals as opposed to in the present study. In our study we also noted that Propofol group could climb upstairs and downstairs as early as 88 min compared to Thiopentone group, who took 154 min for the same. Propofol group was also successful in actively transferring from operating table to recovery bed as compared to Thiopentone group.

Restoration to “street fitness” requires patients to recover psychomotor and cognitive functions to the pre-anesthetic state. A simple task of crossing a road as it appears to be is not so simple especially after anesthesia, as one has to observe signals, discriminate various sound frequencies, and have intact gross and fine motor skills and reaction time. Of the various tests that have been introduced to assess the cognitive and psychomotor functions of post-anesthetic patients to date, the critical flicker fusion test (CFFT), choice reaction time (CRT) test, and driving simulator test are reported as some of the most accurate ones (26,27). However, these tests are cumbersome because they require the post-anesthetic patients to get out of bed and sit in front of a computer screen. Selection of the right combination of psychomotor tests was a crucial point of this study.

Psychomotor tests simulating day to day skillful activities, simple to understand and follow, assessing all aspects of recovery namely memory, attention, concentration, speed, auditory and visual perception, manual dexterity, visuo-motor and auditory motor coordination and simple reaction time. In the present study a battery of 7 psychomotor tests were carefully designed and standardized after observing their performance in 50 pilot patients.

Mail box test assessed manipulative skills both fine and gross motor and visual spatial functioning was a modified version of the basic Purdue peg board test. In 1965 Vickers et al used peg board and found Thiopentone to have delayed recovery till 105-120 minutes (28). Propofol group recovered completely by 1 hr in mail box test, however Thiopentone group remained impaired at 4 hrs. 2nd, 3rd and 4th hr readings in Propofol group were better than their baseline readings. An explanation to this observation can be the practice factor as patients performed each test 3 times preoperatively and 6 times post operatively. If practice factor is eliminated the
imperative in Thiopentone group could have been worse than observed. Manual dexterity test measured hand-eye coordination and concentration requiring visual and sensory processing in brain. Sander et al found Thiopentone group had increase in errors in performing dexterity task at 1 hr and impairment lasting till next day, while Propofol performed better than baseline (p<0.000). In the present study Propofol group recovered completely by 1st hr and Thiopentone remained impaired at 4th hr. To assess the time for which impairment lasts in Thiopentone group, one has to study beyond 4 hrs, which was a limitation of our study. At aiming test (hand-eye coordination and speed) Propofol took 2 hrs to recover to baseline compared to Thiopentone group which remained impaired at 4th hour and could barely aim 60% in first hr. Aiming test showed largest decline in scores in both groups in first 3 hrs, hence proved to be one of the most sensitive test to detect residual effects of drugs used. At Trieger dot test we observed that Propofol group was impaired only till 1st hr and had a better grip of pen with a smooth writing on paper. Practice factor noticed at this test could have been eliminated by presenting different geometric figures instead of a monotonous figure every time. Another limitation of our study was that we could have measured the distance in mm from dots missed to increase the sensitivity of test. DSST test measured recoding skills and recognition of sensory (visual) information, mental concentration, fine muscular coordination and ability to alter eye fixation. Propofol group was impaired at DSST for 1 hr post operatively compared to Thiopentone group which remained impaired significantly at 4 hrs (P < 0.000). Recent memory was assessed in the form of pictorial recall, where patients recalled three picture cards they picked from a set of 15 after memorizing them for 10 min. In a previous study immediate memory was assessed using digit span. Propofol group had a correct digit span recall by 1st hr as compared to Thiopentone took 4 hrs to recall correctly. Visual (picture card) recall test used in our study was unimpaired for all 100 patients irrespective of the anesthetic agent used. Perhaps, both Thiopentone and Propofol had no major effects on short term memory. Another possibility was the simplicity of test or our anticipation of amnesia time was incorrect. Auditory motor coordination test assessed reaction time, auditory perception, attention and motor coordination. Propofol group did not have any impairment at 1 hr post operatively but Thiopentone group remained significantly impaired at 4th hr (p<0.000). To improve the sensitivity of this test, we could use different frequencies of sounds instead of a constant ring. Further accuracy of discrimination should also be assessed by reducing the intervals of sounds heard.

The more predictable and rapid recovery (early and intermediate) after Propofol anesthesia as demonstrated in our patients has strengthened the advantage of using Propofol for short duration outpatient surgeries effectively. Propofol has proved its excellence over Thiopentone with significantly less post operative complications. The incidence of giddiness and nausea, vomiting was significantly high in Thiopentone group compared to Propofol. Though, the use of halothane in some Thiopentone cases makes it a little difficult to prove the true advantage of Propofol as an antiemetic in this study. Also the use of nitrous oxide in Propofol group could have blunted any beneficial antiemetic effect of Propofol.

Finally, it is an important decision of an anesthesiologist in making a choice of anesthetic technique resulting substantial effect on the post operative recovery and discharge for home. Propofol has proved to have an early awakening and intermediate recovery with respect to complete psychomotor recovery. Propofol patients were more alert, could be transferred easily and earlier from operating room to recovery, thus improving the overall efficiency in the busy operating room. The most crucial part of recovery is the psychomotor and cognitive functions recovery. Propofol patients reached 100% of baseline scores in 1 hr at mailbox, manual dexterity and auditory motor coordination and in 2 hrs at DSST, Aiming and Trieger dot. The study can be criticized for two reasons, one was the impairment in Thiopentone group could have been studied further to exactly pin point its duration and secondly practice factor seen in three psychomotor tests namely manual dexterity, mail box and Trieger dot could not be eliminated. Though DSST, Aiming and auditory motor coordination tests proved to be sensitive enough to detect any residual drug effects in patients. Propofol patients could sit without support in 26 min and walk in 84 minutes, for Thiopentone it took 45 minutes to sit and 141 minutes to walk without support. Thus, it appears that Propofol is of significantly greater benefit in fast tracking bypassing PACU and a safe and secure discharge for home to the level of street fitness.

References
Time course of psychomotor, cognitive and ambulatory recovery after Propofol day case Anesthesia: A randomized double blind study.

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