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Effects of Propofol-Thiopental Sodium Admixture on Hypnotic Dose, Pain on Injection and Hemodynamic Responses During Induction of Anesthesia

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Abstract: In this study we compared the effects of four different admixtures of propofol and thiopental sodium on hypnotic dose, pain on injection and hemodynamic responses during induction of anesthesia in 124 ASA class I and II aged 25-55 years patients. In group P_{100}: propofol 1% 20 mL, in group P_{75}: propofol 1% 15 mL thiopental sodium 2.5% 5 mL, in group P_{50}: propofol 1% 10 mL thiopental sodium 2.5% 10 mL and in group T_{100} : thiopental sodium 2.5% 20 mL were used. After premedication with fentanyl 1.5 μg kg^{-1}, induction agent was injected at a rate of 20 mL min^{-1}. Pain on injection after 10 sec and hemodynamic responses at zero, first, third and fifth minutes after induction were recorded and analyzed. Results showed that the required induction dose of admixtures had an additive interaction. Thiopental sodium resulted in more rapid induction of anesthesia than P_{100} and P_{75} ($p = 0.016$ and $p = 0.046$). Pain on injection in P_{50} and P_{75} were less than P_{100} ($p = 0.0001$) and in P_{50} was less than P_{75} ($p = 0.009$). Between subject differences were significant for Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) in P_{100} compared with other groups ($p<0.05$). There were no significant differences in Heart Rate (HR) at T_0, T_3 between four groups but HR was lower in P_{100} compared with P_{50} and P_{75} at T_1 and T_5 ($p<0.05$). Admixture of thiopental sodium with propofol results an additive hypnotic effect, reduces pain of injection and hemodynamic responses compared with propofol injection alone.

Key words: Propofol, thiopental sodium, pain, hemodynamic responses

INTRODUCTION

Propofol, an intravenous anesthetic agent, while associated with a faster recovery compared with thiopental sodium, has some disadvantages. Propofol alone is often accompanied by sever pain on injection, which can be reduced by admixture with lidocaine (John *et al*., 1990) or, prior administration of thiopental sodium (Agrawal *et al*., 2004; Jones *et al*., 1999; Lee *et al*., 1990), ephedrine (Cheong *et al*., 2002), or other drugs. Propofol occasionally induces marked and prolonged hypotension where as hypotension with thiopental sodium induction is less and when occurs, is of shorter duration (Peacock *et al*., 1995). Propofol-thiopental sodium admixture are physico-chemically compatible and also some degree of synergism has been reported when they are administered sequentially (Prankerd and Jones, 1996; Naguib and Sari-Kouzel, 1991). In another studies additive effects has been reported when two drugs are admixtured (Jones *et al*., 1999; Vinik *et al*., 1999).

The aim of this study was to describe the effect of propofol-thiopental sodium admixture on dose required for hypnosis, that is additive or hypnotic, pain on injection with different concentration of propofol and changes in hemodynamic responses during induction of anesthesia.

MATERIALS AND METHODS

This double blinded and randomized clinical trial, was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences in 2005. After the institutional review board approval and informed consent were given, 124 ASA physical status I or II patients aged 25-55 years, scheduled for elective surgeries under general anesthesia were admitted to the study.

The patients were randomized into four groups by a computer generated randomization list that was drowned by the statistician and the sequences were concealed until interventions were assigned. Exclusion criteria included pregnancy, history of drug sensitivity and any side effect after drugs injection which required specific intervention.

After starting standard monitoring of ECG, NIBP and pulse oximeter in operating room, a 20 Gauge IV cannula were inserted on dorsum of each hand separately. One hand for evaluation of induction agent pain and the other for serum infusion or injection of other drugs. Patients

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received in a double blinded manner (both the anesthesiologist and the patient) one of the following induction admixture:

Group P_{100} received propofol 1% (Amp 20 mL, Dongkook Pharm. Co, Ltd) 20 mL (200 mg).

Group P_{75} received propofol 1% and thiopental sodium 2.5% (Vial 1 g, Biochemie GmbH, Kundl-Austria) mixture in the ratio 15 mL (150 mg) to 5 mL (125 mg).

Group P_{50} received propofol 1% and thiopental sodium 2.5% mixture in a ratio 10 mL (100 mg) to 10 mL (250 mg). Group T_{100} received thiopental sodium 2.5%, 20 mL (500 mg).

Induction solutions were prepared by an independent technician in a 20 mL syringe with an envelope. Syringes were loaded into a syringe pump (Graseby 3400, Graseby, Watford. UK) and the connection tubing primed prior to connection. All patients were given 5 mL kg^{-1} lactated ringer solution and premedicated with fentanyl 1.5 μg kg^{-1} intravenously before induction of anesthesia. After 60 sec, induction agent injected at a rate of 20 mL min^{-1}. At 10th second during injection, the patient was asked for any hand discomfort according to Verbal Analog Scale (VAS) that was explained for him/her before anesthesia and the answer was recorded. The infusion was continued until the patient had no verbal response, then the volume of induction agent, was recorded. Atracurium 0.5 mg kg^{-1} was administered to facilitate tracheal intubation and mechanical ventilation. After intubation, anesthesia was maintained with halothane 0.6% in nitrous oxide and 50% oxygen. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Heart Rate (HR) were recorded before any drug administration as base line and before injection of induction solution (T_0) and one (T_1), three (T_3) and five (T_5) minutes after that.

After calculation of induction agent volume, Mean dose concentration for each patient was fitted to the following Equation:

$$\text{Induction Dose (mg)} = [N/100 \times P] + [(100\text{-}N)/100 \times T]$$

P = The amount of propofol alone (mg) for induction of anesthesia

T = The amount of thiopental sodium alone (mg) for induction of anesthesia

N = Volume percent of each drug in the admixture

Sample size was calculated to detect 15 mmHg difference in reduction of systolic blood pressure (SD = ±13 mmHg) after drug-mixture administration with α = 5% (one tailed) and power = 95% and using Bonferroni correction. Statistical analysis was performed with SPSS package (SPSS Inc, Chicago, II, USA). Normality of distribution was checked by Kolmogorov-smirnov test.

Data were analyzed by one way ANOVA, Tukey, Chi square, Repeated measures ANOVA tests when appropriate. $p<0.05$ was considered statistically significant.

RESULTS

There were no significant differences in patient's demographic data between the four groups (Table 1) (one way ANOVA, Chi-square).

In group P_{50} only one patient (3%) and in P_{75} and P_{100}, 5 (16.1%) and 15(48.39%) patients had pain score ≥5 on injection, respectively. No patient in T_{100} had pain score ≥5. Mean pain score according to VAS were 0.11, 1.28, 2.48, 4.71 in T_{100}, P_{50}, P_{75} ,P_{100}, respectively ($p = 0.0001$, one way ANOVA). Pain on injection in P_{50} and P_{75} were statistically less than P_{100} ($p = 0.0001$, Tueky) and in P_{50} was less than P_{75} ($p = 0.009$, Tukey)

Time to hypnosis, volume and dose of induction agent are presented in Table 2.

Time to hypnosis in T_{100} compared with P_{100} and P_{75} was faster ($p = 0.016$ and $p = 0.046$, one way ANOVA). Time to hypnosis difference in P_{50} compared with P_{75} and P_{100} was not statistically significant (Tukey).

The doses required for induction of anesthesia with propofol or thiopental sodium alone (P_{100} and T_{100}) were 2.33 and 5.07 mg kg^{-1}, respectively. With reduction in concentration of one drug in 100% admixture, concentration of the other drug should be raised to have the same effect for hypnosis (induction dose equation), that suggests this dose-effect relationship to be additive. Diagram of popofol and thiopental sodium doses in admixture component required to induce anesthesia was a straight line, which supported this additive effect of two drugs (Fig. 1).

Baseline hemodynamic responses before any drug administration had no significant differences between the four groups (one way ANOVA).

Comparing hemodynamic responses at T_0, T_1, T_3, T_5, between four groups are presented in Fig. 2-4.

Table 1: Comparing demographic data between the four groups

	T_{100}(n = 31)	P_{50}(n = 31)	P_{75}(n = 31)	P_{100}(n = 31)
Sex (M/F)	17/14	14/17	15/16	17/14
Age (year)*	37.5±11.6	31.6±6.3	36.4±10.4	33.2±7.8
Weight (kg)*	69.5±8.33	67.6±9.6	69.8±8.2	68.3±10.2
ASA class (I/II)	27/4	29/2	27/4	29/2

*Mean±SD, no significant differences were observed between the groups

Table 2: Time to hypnosis, volume and dose of induction agents in four groups

	T_{100}	P_{50}	P_{75}	P_{100}
Time to hypnosis (second)	42.5±5.9	44.4±7.6	45.7±6.6	47.9±8.2
Volume of induction agent (mL)	14.1±1.9	14.8±1.9	15.2±2.1	15.8±2.5
Dose of induction agent Propofol/Thiopental sodium (mg)	0/354.2±49.1	74.0±12.6/185.1±31.7	114.0±16/95±13.3	158.7±25.8/0

Data presented as Mean±SD

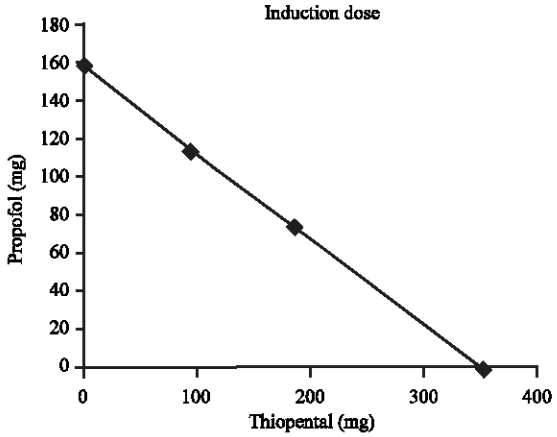

Fig. 1: Diagram of propofol and thiopental sodium doses in admixture compound required to induce anesthesia

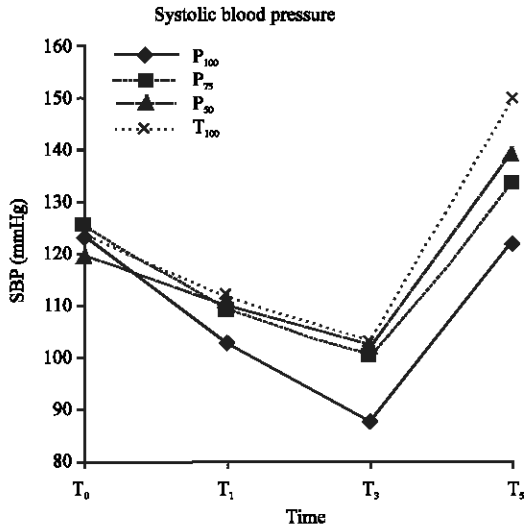

Fig. 2: Comparing Systolic Blood Pressure (SBP) between four groups before and first, third and fifth minutes after induction

Between subject differences were significant for SBP, DBP in P_{100} compared with other groups ($p<0.05$, repeated measures ANOVA) (Fig. 2-4).

There were no significant differences in HR at T_0, T_3 between four groups.

HR was significantly lower in P_{100} compared with P_{50} and P_{75} at T_1 and T_5 ($p<0.05$) (Fig. 3).

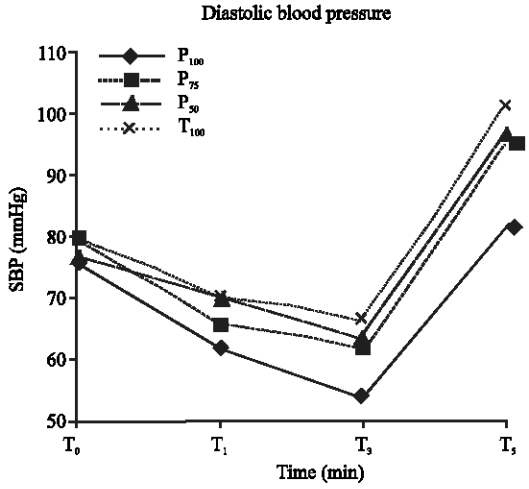

Fig. 3: Comparing Diastolic Blood Pressure (DBP) between four groups before and first, third and fifth minutes after induction

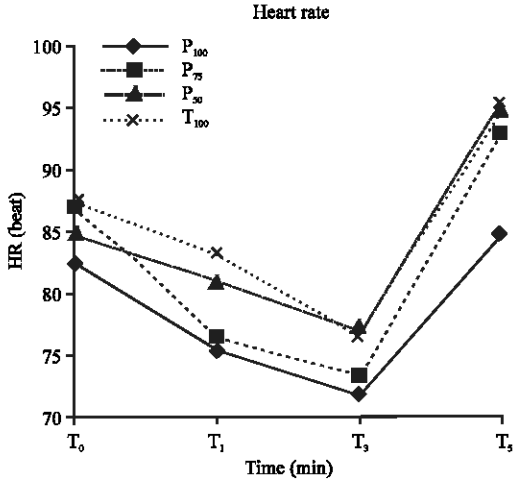

Fig. 4: Comparing Heart Rate (HR) between four groups before and first, third and fifth minutes after induction

DISCUSSION

The current study demonstrates that adding thiopental sodium to propofol for induction of anesthesia results less injection pain and hemodynamic changes during induction of anesthesia.

The hypnotic effect of propofol/thiopental sodium admixture was additive that was correlated with findings of Jones *et al.* (1999) and Vinik *et al.* (1999). It was different with results of Naguib and Sari-Kouzel (1991) which found synergistic interaction. The different results may be due to different manner of administration of the two drugs (sequential rather than mixing drugs) in the last study. However the similar binding sites on the amino butyric acid-A (GABA-A) receptors for propofol and barbiturates may suggest an additive rather than synergistic relationship.

As we noted previously, adding thiopental sodium to propofol, reduced injection pain. Pain during injection in P_{50} was less than P_{75} and in P_{75} was less than P_{100} group. Admixture of propofol and thiopental sodium produced solution with a pH close to that of thiopental sodium and lowered the concentration of propofol (Stanski *et al.*, 1983). Furthermore, maximum injection rate was 20 mL min^{-1} resulting 40 to 60 sec rather than the usual administration time of 20 sec. These changes may modify the propofol induced pain on injection that was correlated with Jones *et al.* (1999) and Agrawal *et al.* (2004).

Time to hypnosis in T_{100} was faster than P_{100} and P_{75} and reduction in SBP and DBP were attenuated by propofol admixture with thiopental sodium when compared to P_{100} that was correlated with Jones *et al.* (1999) study.

This study showed that HR reduction in P_{100} was more than P_{50}, P_{75} and T_{100} at T_1 and T_5 but Jones *et al.* (1999) found no significant difference in HR between their groups.

In conclusion this study showed that propofol-thiopental sodium admixture is a suitable drug composition for induction of anesthesia, attenuation of injection pain and reduction of hemodynamic changes compared with using propofol alone. These effects are probably multifactorial in origin and the exact mechanism especially pain reduction with propofol needs further evaluation.

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REFERENCES

Agrawal, A., M.F. Ansari and D. Gupta *et al.*, 2004. Pretreatment with thiopental for prevention of pain associated with propofol injection. Anesth. Analg., 98: 683-686.

Cheong, M.A., K.S. Kim and W.J. Choi, 2002. Ephedrine reduces the pain from propofol injection. Anesth. Analg., 95: 1293-1296.

John, R.A., N.J.N. Harper and S. Chadwick *et al.*, 1990. Pain on injection of propofol. Methods of alleviation. Anesthesia, 45: 439-442.

Jones, D., R. Prankerd and C. Lang *et al.*, 1999. Propofol-thiopentone admixture-hypnotic dose, pain on injection and effect on blood pressure. Anesth. Intensive Care, 27: 346-356.

Lee, T.W., A.E. Loewenthal and J.A. Strachan *et al.*, 1994. Pain during injection of propofol-The effect of prior administration of thiopentone. Anesthesia, 49: 817-818.

Naguib, M. and A. Sari-Kouzel, 1991. Thiopentone-Propofol hypnotic synergism in patients. Br. J. Anesth., 67: 4-6.

Peacock, J.E., A. Blackburn and K.M. Sherry *et al.*, 1995. Arterial and jugular bulb blood propofol concentration during induction of anesthesia. Anesth. Analg., 80: 1002-1006.

Prankerd, R. and R.D.M. Jones, 1996. The physicochemical compatibility of injectable propofol-thiopental sodium admixture. Am. Health Sys. Pharm., 53: 2606-2610.

Stanski, D.R., P.G. Burch and S. Harapat, 1983. The pharmacokinetics and anesthetic potency of a thiopental isomer. Pharm. Sci., 72: 937-940.

Vinik, H.R., E.L. Brandley and I. Kissin, 1999. Isobolographic analysis of Propofol-thiopental sodium hypnotic interaction in surgical patients. Anesth. Analg., 88: 667.