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Propofol and Postoperative Pain: Systematic Review and Meta-Analysis

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1. Introduction

If an intravenous or inhalator anesthetic, would include in itself all the components of general anesthesia, like hypnoses, analgesia, amnesia etc. it would represent a really ideal anesthetic.

Propofol is the drug of choice for induction and/or maintenance of anesthesia and sedation in the operating room and intensive care unit. It is a short-acting intravenous anaesthetic that features high blood-tissue solubility and allows a rapid induction and rapid emergence. Propofol has γ-aminobutyric acid agonist activity and produces dose dependent central nervous system depression resulting in sedation and hypnosis.

Analgesic properties of propofol are discussed in many studies, in recent years. However, evidence suggesting that the drug possesses analgesic activity still remains questionable (Fassoulaki, 2011).

The objective of this study is to systematically determine the effects of propofol in postoperative pain.

We have included double-blind, randomized, and controlled trials in humans, where postoperative analgesic effect of propofol was compared with another anesthetic or non-drug intervention.

The study was carried out according to the methods recommended by the Cochrane Collaboration (Higgins et al., 2009) and written in accordance with the PRISMA statement for reporting systematic reviews (Liberati et al., 2009, Moher et al., 2009).

Reports of randomized controlled trials were systemically sought using the Cochrane Library, PubMed, Embase, www.clinicaltrials.gov, and hand searching from the reference lists of identified papers.

Data were analyzed from 25 randomized controlled trials totaling 2033 adults and children. We developed standard data collection sheets to record details of trial design, interventions, and outcome measures for every trial. We extracted information about propofol and control group. Information about number of patients enrolled, type of surgical intervention and side effects, were also noted. Data on postoperative pain relief using pain scores time to first analgesic request and consumption of supplementary analgesics was taken from each report.

Qualitative analysis of postoperative effectiveness was evaluated by significant difference ($P < 0.05$ as reported in the original investigation) in pain relief using pain scores, time to

first analgesic request, and consumption of supplementary analgesics between the treatment groups, and by assessment of the clinical importance of observed differences.

Quantitative analyses of combined data were intended by calculation of the number of patients reporting any pain or no pain (pain response rate) between treatment groups.

Each trial was assessed for different measures of internal sensitivity. First, trials were checked for magnitude of pain intensity. Because it is difficult to detect an improvement with low or no pain, it was noted that pain scores were less than 30 mm on a visual analog scale (VAS) or less than moderate pain on a verbal rating scale or similar score. Second, it was noted that a power calculation of the statistical tests was performed. Trials with sample sizes less than 10 patients per treatment group were not considered in the study.

Meta-analyses were carried out by direct comparisons of intervention versus control and indirect comparisons between the networks of interventions shown to be significant individually.

2. Propofol

Propofol (2,6-diisopropyl phenol) is chemically inert phenolic compound with anesthetic properties. It has high lipid solubility, but is almost insoluble in water. The original preparation contained the solubilizing agent Ctenophore EL (polyethoxylated Castrol oil). Reformulation of the drug in an egg-oil-glycerol emulsion has eliminated hypersensitivity reactions that occurred with the original formulation (Sebel, 1989). The dose of propofol required to induce anesthesia measured by loss of eyelash reflex in 95% of healthy unpremedicated patients was 1.5-2.5 mg/kg. The range of induction times was 22-125 seconds. The rapid loss of consciousness was realized due to the immediate uptake of the lipid – soluble drug by the central nervous system (CNS).Within several minutes of intravenous administration, the plasma concentration of propofol decreases due to the distribution of the drug throughout the body and its uptake by peripheral tissues. As the plasma concentration falls, propofol diffuses from the CNS into the systemic circulation; when bolus doses of the anesthetic are used to induce anesthesia, there is a rapid recovery of full consciousness and awareness. These advantageous properties have contributed to the popularity of propofol as an induction agent for short procedures and day – case surgery (Short, 1999).

Propofol is also indicated for the maintenance of anesthesia computer-assisted continuous infusion and target-controlled infusion of propofol using a monitor of the hypnotic effects of propofol on the brain electroencephalographic Bispectral Index [BIS] monitor; it is possible to create a closed-loop delivery system for improving the titration of propofol during general anesthesia (Kwan, 1989, Singh, 1999).

Infusions of subanesthetic doses of propofol have been used to sedate patients for surgery under regional anesthesia, in diagnostic centers for sedation during gastroenterology and pulmonary medicine procedures, as well as in critical care areas for sedation of ventilator-dependent patients as an alternative to benzodiazepines and/or opioid analgesics (Mazurek, 2004).

Propofol is extensively bound to plasma proteins; approximately 97-98% is bound to albumin. After intravenous injection the plasma concentration of propofol decline. The initial fall is extremely rapid (half life 1-3 min), reflecting the distribution of the lipid - soluble drug from plasma to tissue.

Approximately 70% of a dose is excreted in the urine within 24 hours after administration, and 90% is excreted within 5 days. Clearance of propofol ranges from 1.6 to 3.4 liters per minute in

healthy 70 kg patients. As the age of the patient increases, total body clearance of propofol may decrease. Clearance rates ranging from 1.4 to 2.2 liters per minute in patients 18 to 35 years of age have been reported, in contrast to clearance rates of 1 to 1.8 liters per minute in patients 65 to 80 years of age. The propofol mean total body clearance rate was 2.09 +/- 0.65 1/min (mean SD), the volume of distribution at steady state was 159 +/- 57 I, and the elimination half-life was 116 +/- 34 min. Elderly patients (patients older than 60 yr) had significantly decreased clearance rates (1.58 +/- 0.42 vs. 2.19 +/- 0.64 1/min), whereas women (vs. men) had greater clearance rates (33 +/- 8 vs. 26 +/- 7 1 kg^{-1} min^{-1}) and volumes of distribution (2.50 +/- 0.81 vs. 2.05 +/- 0.65 1/kg). Patients undergoing major intraabdominal surgery had longer elimination half-life values (136 +/- 40 vs. 108 +/- 29 min). Patients required an average blood propofol concentration of 4.05 +/- 1.01 µg/ml for major surgery and 2.97 +/- 1.07 g/ml for nonmajor surgery. Blood propofol concentrations at which 50% of patients were awake and oriented after surgery were 1.07 and 0.95 µg/ml, respectively. The metabolic clearance of propofol exceeds hepatic blood flow, which has leaded to suggestion that propofol is also metabolized in extrahepatic sites. Approximately 70% of a dose is excreted in the urine within 24 hours after administration, and 90% is excreted within 5 days. Psychomotor performance returned to baseline at blood propofol concentrations of 0.38-0.43 g/ml (Shafer et al., 1988, White, 1989, Deegan, 1992; Zuppa et al., 2003).

Propofol causes a significant reduction in systemic blood pressure (more than 50% of preoperative level). This increase in blood pressure is a result of decrease in systemic vascular resistance. In addition to arterial vasodilatation, propofol produces venodilation (due both to a reduction in sympathetic activity and to a direct effect on the vascular smooth muscle), which contributes to its hypotensive effect. The fall in cardiac output is manifested with decrease in heart rate. (Machała & Szebla, 2008; Frolich, 2011).

Respiratory depression and apnea are more pronounced with propofol than thiopental. Propofol decreases tidal volume and increases respiratory rate. The ventilatory response to carbon dioxide and hypoxia is also significantly decreased, but propofol does not inhibit hypoxic pulmonary vasoconstriction. Propofol can produce bronchodilation in patients with chronic obstructive pulmonary disease and in patients with acute laryngospasm during emergence from anesthesia (Zeller et al., 2005).

Propofol decreases CMRO2 and CBF, as well as ICP.33 However, when larger doses are administered, the marked depressant effect on systemic arterial pressure can significantly decrease CPP. Cerebrovascular autoregulation in response to changes in systemic arterial pressure and reactivity of the cerebral blood flow to changes in carbon dioxide tension are not affected by propofol. Evidence for a possible neuroprotective effect has been reported in vitro preparations, and the use of propofol to produce EEG burst suppression has been proposed as a method for providing neuroprotection during aneurysm surgery. Its neuroprotective effect may at least partially be related to the antioxidant potential of propofol's phenol ring structure, which may act as a free-radical scavenger, decreasing free-radical induced lipid peroxidation. Recent studies reported that this antioxidant activity may offer many advantages in preventing the hypoperfusion/reperfusion phenomenon that can occur during surgery (Dagal & Lam, 2009; Girard et al., 2009; Ozturk et al., 2009; Menku et al., 2010).

Propofol produces cortical EEG changes that are similar to thiopental. However, sedative doses of propofol increase â-wave activity analogous to the benzodiazepines. Induction of anesthesia with propofol is occasionally accompanied by excitatory motor activity (so-called nonepileptic myoclonia). In a study involving patients without a history of seizure disorders, excitatory movements following propofol were not associated with EEG seizure activity.

Propofol appears to possess profound anticonvulsant properties. Propofol has been reported to decrease spike activity in patients with cortical electrodes implanted for resection of epileptogenic foci and has been used successfully to terminate status epilepticus. The duration of motor and EEG seizure activity following electroconvulsive therapy is significantly shorter with propofol than with other IV anesthetics. Propofol produces a decrease in the early components of somatosensory and motor evoked potentials but does not influence the early components of the auditory evoked potentials (Modica et al., 1990).

There is no evidence to suggest that propofol has any significant effects on renal or hepatic function.

Propofol is known to possess direct antiemetic effects. Its use for induction and maintenance of anesthesia has been shown to be associated with a lower incidence of postoperative nausea and vomiting (PONV) when compared to any other anesthetic drug or technique. The precise mechanism of propofol antiemetic effect of propofol has not been elucidated, several mechanisms have been proposed, including a direct depressant effect on the chemoreceptor trigger zone (CTZ), the vagal nuclei, and other centers implicated in PONV (Becker, 2010). A systematic review of PONV following maintenance of anesthesia with propofol or an inhalational anesthetic agent found that patients receiving propofol had a significantly lower frequency of PONV, regardless of induction agent, choice of inhalational agent, use of nitrous oxide, patient age, or use of an opioid (Soppitt et al., 2000). Another systematic review found that propofol may be effective in reducing PONV in the short term, but only when given as a continuous infusion for maintenance of anesthesia and when the PONV event rate is greater than 20% (Eberhart et al., 2006). There is evidence of a relationship between plasma propofol concentration and antiemetic efficacy. Gan et al., 1999, found that a median plasma propofol concentration of 343 ng/mL was associated with a reduction in PV in surgical patients. After a typical induction dose, plasma propofol levels remain above this antiemetic serum concentration threshold for approximately 30 minutes. Therefore, the common practice of selecting propofol for inducing anesthesia because of its antiemetic effects provides little benefit to a patient in terms of reducing the likelihood that the patient will develop PONV during the stay in the postanesthesia care unit and after discharge from the ambulatory surgery center.

Anticonvulsant effect of propofol is always described (Simpson et al., 1988). Theoretically, propofol should be strongly anticonvulsant, as it exhibits both GABAergic effects and persistent sodium current and calcium current blockade. However, a literature search of propofol associated tonic-clonic seizures retrieved more than 500 case reports, of which 81 were analyzed in more detail. The denominator is missing from these case reports, and hence the true incidence is unknown. Among the 172,592 anesthetics analyzed there were 53 generalized convulsions, of which 16 were thought to be primarily due to anesthesia. Fifteen of these cases were attributed to local anesthetic drug error, anti-epileptic drug withdrawal or cerebral anoxia/hypercarbia. This left a single case where the seizure was thought to be due to the anesthetic, propofol, an incidence of 1 per 172,592 anesthetics (Fredman et al, 1994).

Propofol has a remarkable safety profile (Sarani B, Gracias, 2008). Dose dependent hypotension is the commonest complication; particularly in volume depleted patients. Hypertriglyceridemia and pancreatitis are uncommon complications. Allergic complications, which may include bronchospasm, have been reported. High dose propofol infusions have been associated with the "propofol syndrome"; this is a potentially fatal complication characterized by severe metabolic acidosis and circulatory collapse (Murdoch &, Cohen, 1999). This is a rare complication first reported in pediatric patients and believed

to be due to decreased transmembrane electrical potential and alteration of electron transport across the inner mitochondrial membrane. And, of course pain during injection of propofol which could prevent in several ways (Jalota et al., 2011).

Finally, the favorable pharmacokinetic properties, like short half-life and high clearance rate, minimal side effects and other nonhypnotic positive effects make it safe and usefull in clinical practice.

3. Analgesic effects of propofol

General anesthetics and propofol modulate the function of the gama (γ)-aminobutyric acid (GABA)$_A$ receptors, the inhibitory neurotransmitter receptors in the central nervous system. GABA is the major inhibitory neurotransmitter in the central nervous system, with fast synaptic inhibition mediated by postsynaptic GABA$_A$ receptors. GABA$_A$ receptors are members of the superfamily of ligand-gated ion channels and are thought to consist of five subunits (α, β, and γ). The GABA-induced chloride current can be potentiated by some general anesthetics. The actions of propofol appear to be mediated by β3-containing GABA$_A$ receptors. Specific residue is located within the second transmembrane region of the β3 subunit of the GABA$_A$ receptor and has a influence in determining the action of propofol (Krasowski et. Al., 1998; Siegwart et al. 2002).

The hypnotic effect of propofol and probably analgesic effect is related to GABA accumulation and occupation of the GABA receptor. Occupation of receptors produced hyperpolarisation of the postsynaptic cell membrane and neuronal inhibition. Propofol at low concentration enhance the amplitude of response of GABA and prolong the duration of GABA mediated synaptic inhibition. At supraclinical concentrations propofol directly activate the receptors anion channel.

The analgesic effect of propofol may result as it acts at GABA$_A$ receptors (Dong & Xu, 2002). On the other hand, propofol induced potentiation of glycin receptors at the spinal level and might contribute to its antinociceptive actions and general anesthesia (Xu et al., 2004).

Spinal (NMDA) receptors were reported to be involved in the antinociceptive action of propofol. Prolonged firing of C-fiber nociceptors causes release of glutamate which acts on N-methyl-D-aspartate (NMDA) receptors in the spinal cord. Activation of NMDA receptors causes the spinal cord neuron to become more responsive to all of its inputs, resulting in central sensitization. NMDA-receptor antagonists can suppress central sensitization. NMDA-receptor activation not only increases the cell's response to pain stimuli, it also decreases neuronal sensitivity to opioid receptor agonists. In addition to preventing central sensitization, co-administration of NMDA-receptor antagonists with an opioid may prevent tolerance to opioid analgesia. Was reported that intrathecal administration of an NMDA receptor agonist inhibited the antinociceptive effect of propofol; in contrast, an NMDA receptor antagonist enhanced the antinociceptive action of propofol (Cheng et al., 2008). These studies demonstrated that propofol has a synergistic action with several nociceptive transmission cascades including amino acid and opioid systems in the spinal cord.

The above mentioned methods determined the probable way of analgesic action of propofol.

4. Methods

We followed the PRIZMA statement that recommends standards to improve the quality of reporting of meta-analyses.

Systematic search

The study was carried out according to the methods recommended by the Cochrane Collaboration and written in accordance with the PRISMA statement for reporting systematic reviews (Higgins et al., 2009 & Liberati et al., 2009).

This systematic review included studies published up to December 2010. We conducted a systemic search of the electronic databasas: PubMed, Cochrane Library, and Embase, www.clinicaltrials.gov, and hand searching from the reference lists of identified papers. We used the search terms "propofol" and ("postoperative analgesia" OR "analgesic effect"). Abstracts and unpublished studies were not considered. The search was limited to clinical trials and randomised controlled trials. Reference lists from identified studies and journals which appeared to be associated with the most retrieved citations were then hand-searched. The trials in languages other than English were not excluded. We prepared a flow diagram to summarize the study selection process according to PRISMA (Jaded et al., 1996) (Figure 1.).
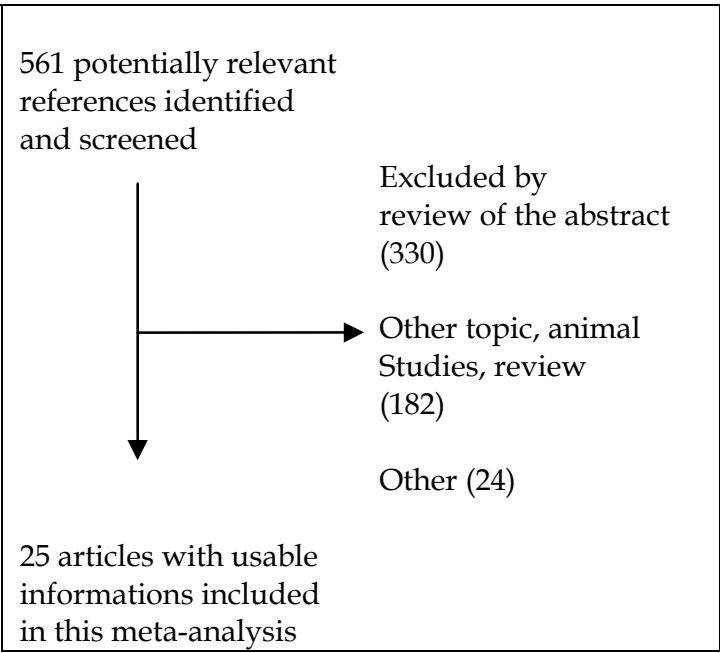

Fig. 1. Flow diagram of excluded and included studies according to PRIZMA statement

To minimize data duplication as a result of multiple reporting we compared papers from the same author. In addition, we searched www.clinicaltrials.gov for studies. Two authors (HJ and AD) screened and retrieved reports and excluded irrelevant studies. Relevant data were extracted by one author (VG) and checked by another (AH).

From each study we extracted details on patients' characteristics (adults and children, ASA status, age), type of surgery or no surgery and use of anesthetics in control group (Table 1.). Pain score, pain score method and use of postoperative analgesics, were also noted (Table 2). Side effects were noted in Table 3.

Study selection

To be considered for the review, the study was evaluated with regard to randomization method, allocation concealment, details of blinding measures, and withdrawals and dropouts using the modified 7-point 4-item Oxford scale (Figure 2) (Dong et al., 2002). This meant that adequate randomization was an absolute requirement for selection. However,

double-blinding was not a requirement, because adequate blinding was not felt to be possible in most studies. Each study was evaluated independently by authors and agreement was reached by consensus.

Selected studies included 25 randomised controlled trials that compared the use propofol during anesthesia and any drug or non-drug intervention, or a combination, with an active or inactive control, and reported the response rate and severity of pain after propofol anesthesia.

VALIDITY SCORE (0-7)	
Randomisation	*Double blinding*
0 None	0 None
1Mentioned	1 Mentioned
2Described and adequate	2 Described and adequate
Concealment of allocation	*Flow of patients*
0 None	0 None
1 Yes	1 Described but incomplete
	2 Described and adequate

Fig. 2. Modified Oxford Scale

Selected studies included 25 randomised controlled trials that compared the use propofol during anesthesia and any drug or non-drug intervention, or a combination, with an active or inactive control, and reported the response rate and severity of pain after propofol anesthesia.

The studies included in this review enrolled 1970, male and female patients, 1 to 80 year old, ASA I-III, who underwent surgical or non-surgical treatment resulting in the need for acute pain control. Relevant pain outcomes included number of patients who express pain, pain intensity, time to first analgesic request and supplemental analgesic demand were noted. All included studies had numerical data presented in the text or a table; if data were not presented as such, we extracted the information from the graphs if the scale allowed a sufficiently precise estimation.

We excluded trials including less than 10 patients and those reporting on chronic pain. Data from animal studies, abstracts, letters or reviews were not considered.

Information on number of patients, anesthetics and type of surgery was obtained from each report.

The data extracted from each of the included trials included: eligibility and exclusion criteria, study design, duration and degree of follow-up, randomization, allocation concealment, blinding, number and characteristics of participants, type of surgery, pain score, time to first analgesic request, and consumption of supplementary analgesics between the propofol and other treatment groups, and by assessment of the side effects (Table 1, 2 & 3).

Meta analyses

Qualitative analysis of postoperative effectiveness was evaluated by significant difference ($P < 0.05$ as reported in the original investigation) in pain relief using pain scores, time to first analgesic request, and consumption of supplementary analgesics between the treatment groups, and by assessment of the clinical importance of observed differences.

Reference	VS	Treatment	Control	No. of Patients	Type of Intervention
Briggs et al. 1982	3	Propofol	Thiopentone	40	Gynecologic procedures
Doze et al. 1988	4	Propofol	thiopental/isoflurane	120	Abdominal surgery
Borgeat et al. 1990	4	Propofol	thiopental/halothane	40	ENT surgery
Anker-Møller et al. 1991	4	Propofol	thiopental/saline	19	laser stimulation
V Hemelrijck et al. 1991	4	Propofol	desflurane	92	gynecological laparascopy
Hendolin et al. 1994	5	Propofol	thiopental/isoflurane	41	uvuloplasty
Jellish et al. 1995	5	Propofol	thiopental/isoflurane	102	middle ear surgery
Petersen-Felix et al. 1996	2	Propofol	alfentanyl	12	electric/laser/acoustical stimulation
Eriksson et al. 1996	5	desflurane	propofol	90	gynecological laparascopy
Zacny et al. 1966	3	propofol	fentanyl	12	ice-cold water
Davis et al. 1997	5	reifentanil	alfentanil/isofl/prop	129	strabismus surgery
Boccara et al. 1998	5	propofol	isoflurane	40	cosmetic abdominoplasty
Ozkose et al. 2001	6	Propofol,/fentanyl	sevoflurane/isofl & alfentanyl	60	laminectomy and discectomy operations
Hand et al. 2001	3	propofol	intralipids	48	tourniquet pain
Mukherjee et al. 2003	6	propofol,fentanyl, isoflurane	pr, remifentanil	100	middle ear surgery
Hofer et al. 2003	7	propofol	sevoflurane	305	gynaecologic or orthopedic procedures
Coolong et al 2003	4	propofol	thiopental	84	laparascopic procedures
Frölich et al. 2005	4	propofol	placebo	80	thermal pain
Cheng et al. 2008	7	propofol	isoflurane	80	open uterine surgery
Fassoulaki et al. 2008	7	sevofl/desfl	propofol	105	gynecological operations
Hasani et al. 2009	5	propofol	halothane	83	abdominal surgery
Bandschapp et al. 2010	7	propofol	intralipid/saline	14	electrical stimulation
Tan et al. 2010	6	propofol	sevoflurane	80	gynecological laparascopic
Pieters et al. 2010	7	propofol	sevoflurane	42	adenotonsillectomy
Shin et al. 2010	7	propofol & remifentanyl	sevoflurane and remifentanyl	214	brest cancer surgery

VS-Validity Score (Modified Oxford Scale)
NS - no significant difference between treatment groups or no significant difference in favor of the treatment;
P< 0.05 - significant difference between treatment groups in favor of the treatment; NE - not evaluated.

Table 1. Details of study included.

References	Pain Score Method	Pain Score	Time to First Analgesic Request	Supplemental Analgesic Demand
Briggs et al. 1982	tibial pressure algesimetry	P<0.001	NE	NE
Doze et al. 1988	NE	NE	p>0.05	p>0.05
Borgeat et al. 1990	VAS	P<0.05	p>0.05	p>0.05
Anker-Møller et al. 1991	laser power meter	NS	NE	NE
Van Hemelrijck et al. 1991	VAS	NS	NS	NS
Hendolin et al. 1994	VAS	P<0.05	NS	NS
Jellish et al. 1995	VAS	NS	NS	NS
Petersen-Felix et al. 1996	VAS	NS	NE	NE
Eriksson et al. 1996	VAS	NS	NS	NS
Zacny et al. 1966	VAS	P<0.05	NE	NE
Davis et al. 1997	OPDS	NS	NS	NS
Boccara et al. 1998	VAS	P<0.05 for Iso	P<0.05 for Iso	P<0.05 for Iso
Ozkose et al. 2001	VAS	P<0.05	P<0.05	P<0.05
Hand et al. 2001	NRS	NE	P<0.05	P<0.05
Mukherjee et al. 2003	VAS	P<0.05	P<0.05	P<0.05
Hofer et al. 2003	VAS	NS	NS	NS
Coolong et al 2003	VNRS	NS	NS	NS
Frölich et al. 2005	VAS	P<0.05 more pain with propofol	NE	NE
Cheng et al. 2008	NAS	p<0.01	p<0.01	p<0.01
Fassoulaki et al. 2008	VAS	NS	NS	NS
Hasani et al. 2009	FPS	NS	NE	NE
Bandschapp et al. 2010	NRS	P<0.05	NE	NE
Tan et al. 2010	VAS	P=0.01	NS	NS
Pieters et al. 2010	CHEOPS	P<0.05	P<0.05	P<0.05
Shin et al. 2010	VAS	P> 0.001	P> 0.001	P> 0.001

NS - no significant difference between treatment groups or no significant difference in favor of the treatment; *P*<0.05 - significant difference between treatment groups in favor of the treatment; NE - not evaluated.

Table 2. Details of study included.

Study	Nauzea Propofol n/N	Control n/N	P	Vomiting Propofol n/N	Control n/N	P	Other side effects Propofol n/N	Control n/N	P
Doze 1988	1/ 60	8 /60	P<0.05	3/ 60	16/60	P<0.05	10 në 60	34/60	P<0.05
Borgeat 1990	0/20	2/20	NS	0/20	2 në 20	NE	16/20	20/20	P<0.05
Vhemelrijck 1991			P<0.05			P<0.05	9/46	46/46	P<0.05
Hendolin 1994	0/20	2/21	NS	0/20	1/21		2/21	2/21	NS
Jellish 1995	3/34	20/68	P<0.05	5/34	15/68	NS			
Eriksson 1996			NS			NS			NS
Davis 1997				6/20	32/57	P<0.05	0/20	23/57	P<0.05
Boccara 1998	5/ 20	12/ 20	P<0.05						NS
Ozkose 2001				1 /20	22/40	P<0.05			
Mukherjee 2003			NS			NS			NS
Hofer 2003	50/155	75/146	P<0.001	34/155	50/146	P<0.01			
Coolong 2003			NS			NS			NS
Cheng 2008			NS			NS			NS
Hasani 2009			NS			NS			NS
Tan 2010			NS			NS			NS
Pieters 2010	1/19	7/19	P<0.05	1/19	7/19	P<0.05			NS
Shin 2010	29/96	40/90	P<0.005	29/ 96	40/90	P<0.005	50/96	42/90	NS

NS - no significant difference between treatment groups or no significant difference in favor of the treatment;

P<0.05 - significant difference between treatment groups in favor of the treatment; NE - not evaluated.

Table 3. Details of study included (side effects).

Quantitative analyses of combined data were intended by calculation of the number of patients reporting any pain or no pain (pain response rate) between treatment groups. For studies with multiple intervention groups, we partitioned the count of events and patients in the control group into two or more control groups within any meta-analysis to avoid a unit of analysis error. For the studies participating in the indirect comparisons, we partitioned the comparator group according to how many times it was used for indirect comparisons (across meta-analyses). The summary relative risks and 95% confidence intervals were estimated using a random effects Mantel-Haenszel method in RevMan 5.0 (Cochrane Collaboration). Statistical heterogeneity was assessed by the I^2 value.

The weight given to each study in this analysis (*i.e.*, how much influence each study had on the overall results) was determined by the precision of its estimate by taking into account study size and SDs of the pain in the individual trials. For the current use, a mean for each treatment group was calculated in every trial from all available recordings performed after anesthesia with propofol. Verbal rating pain scores and similar scores were converted to VAS pain scores (*e.g.*, a four-point verbal rating score including no, light, moderate, and severe pain was converted to 0, 25, 50, and 75 mm VAS, respectively).

5. Results

The systematic search in the databases identified 561 relevant articles. After screening, 25 studies potentially met the inclusion criteria. The full-text publications of these studies were examined in more detail. Four study was excluded, because it was reviews or editorial articles. In 90 studies the subject of investigation were animals and also were excluded. (Fig. 1).

The data of 25 randomized controlled studies were included in the present meta-analysis (Table 1,2 &3). A total of 1970 patients (909 with propofol), male and female were included. The patients were 1-85 year old. The 294 patients were children, aged 1-18 year (Borgeat et al.,1990, Pieters et al., 2010, Davis et al., 1997 & Hasani et al., 2009). The participans undergoing brest, ginecologic, orthopedic, ENT, abdominal, urogenital, spine, cosmetic or eye surgery. In 7 studies the participants were volunteer and have no surgery (total 163 volunteers) (Briggs et al., 1982, Anker-Møller et al., 1991, Zacny et al., 1996, Petersen-Felix et al., 1996, Hand et al., 2001, Frolich et al., 2005 & Bandschapp et al. ,2010).

The participants were randomly assigned to receive propofol and in control group: thiopental (Briggs et al.,1982 & Coolong et al.,2003); thiopental and saline (Anker-Møller et al., 1991); thiopental with halothane (Borgeat et al.,1990); or, thiopenthal with isoflurane (Doze et al., 1988 , Hendolin et al.,1994 & Jellish et al.,1995). In control grup the inhalation anesthetics used were halothane (Hasani et al., 2009), isoflurane (Boccara et al., 1998& Cheng et al.,2008), sevoflurane (Ozkose et al.,2001, Hofer et al., 2003, Tan et al., 2010, Pieters et al., 2010 & Shin et al., 2010) and desflurane (Van Hemelrijck et al.,1991&Fassoulaki et al., 2010). Also, the control groups contained opioids: fentanyl, remifentanil (Davis et al., 1997, Mukherjee et al., 2003 & Shin et al., 2010) and alfentanil (Petersen-Felix et al., 1996& Davis et al., 1997).

Intensity of pain scores was considered adequate (>30 mm VAS) in all trials. VAS (visual analogue score) pain score was not present in 9 studies. The pain scores used in studies was NRS-numeric rating scale (Hand et al., 2001&Bandschapp et al. ,2010), NAS-Numerical analogue score (Cheng et al., 2008), CHEOPS-Children's Hospital of Eastern Ontario Scale (Pieters et al., 2010), tibial pressure algesimetry (Briggs et al., 1982), VNSR-verbal numeric rating scale (Coolong et al., 2003), laser power meter (Anker-Møller et al., 1991), FPS- faces pain scale (Hasani et al., 2009) and OPDS-Objective Pain Discomfort Scale (Davis et al., 1997).
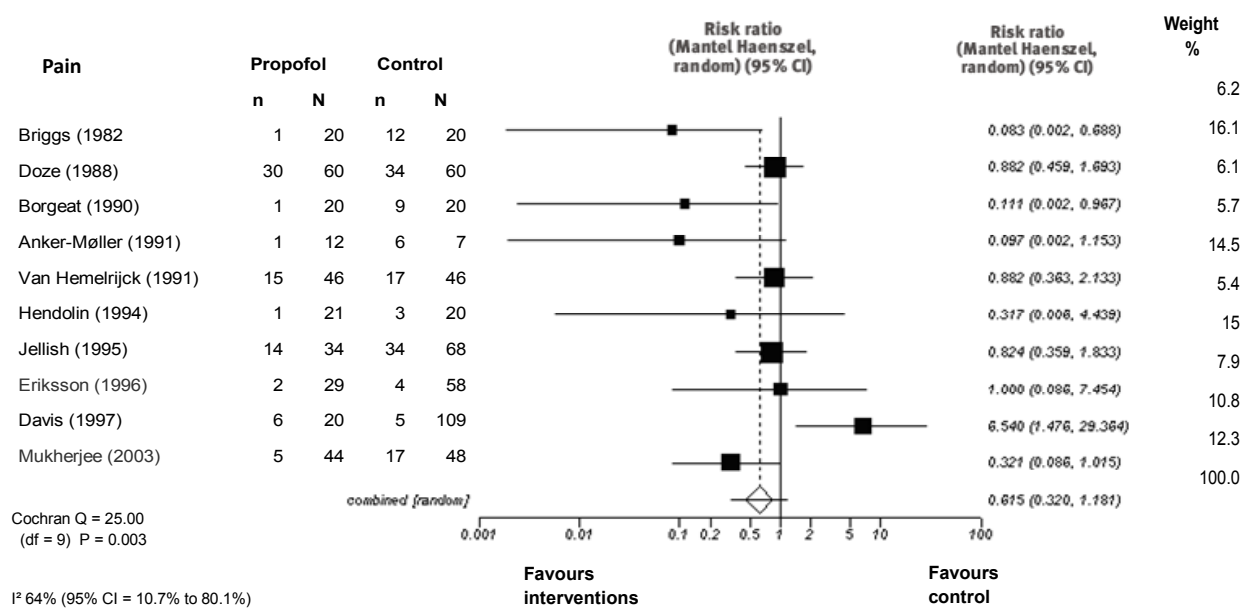

Fig. 3. Risk of postoperative pain after propofol anesthesia.

In selected 25 randomized controlled trials the postoperative pain was evaluated in patients treated with propofol. In 15 of them the degree of pain was given as the mean and, in our research to find risk ratio (Mantel Haenszel, random) we included 10 researches in which pain was expressed as present or absent.

Pain was rarely present in the groups treated with propofol 0.615 (95% CI 0.320-1.181) (Fig. 3).
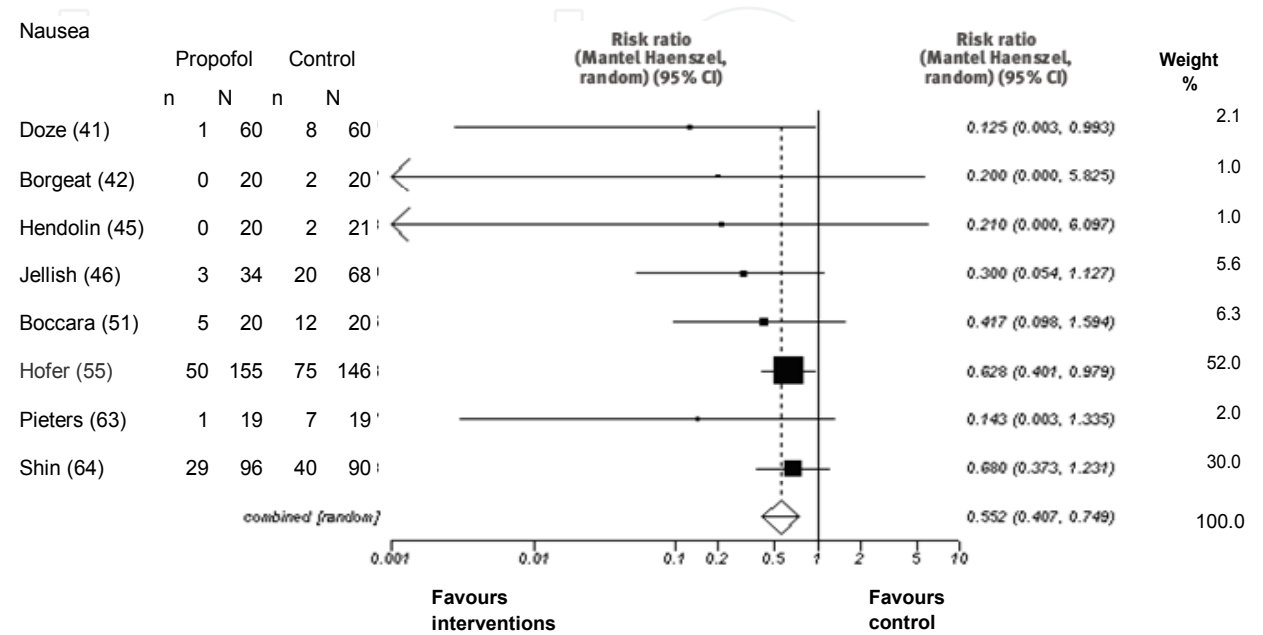

Fig. 4. Risk of postoperative nauzea after propofol anesthesia.

To study the presence of nausea we analyzed eight researches that have investigated this symptom in postoperative period. Nausea was the rare risk ratio 0.552 in intervention group (95% CI 0.407-0.749) (Fig. 4).
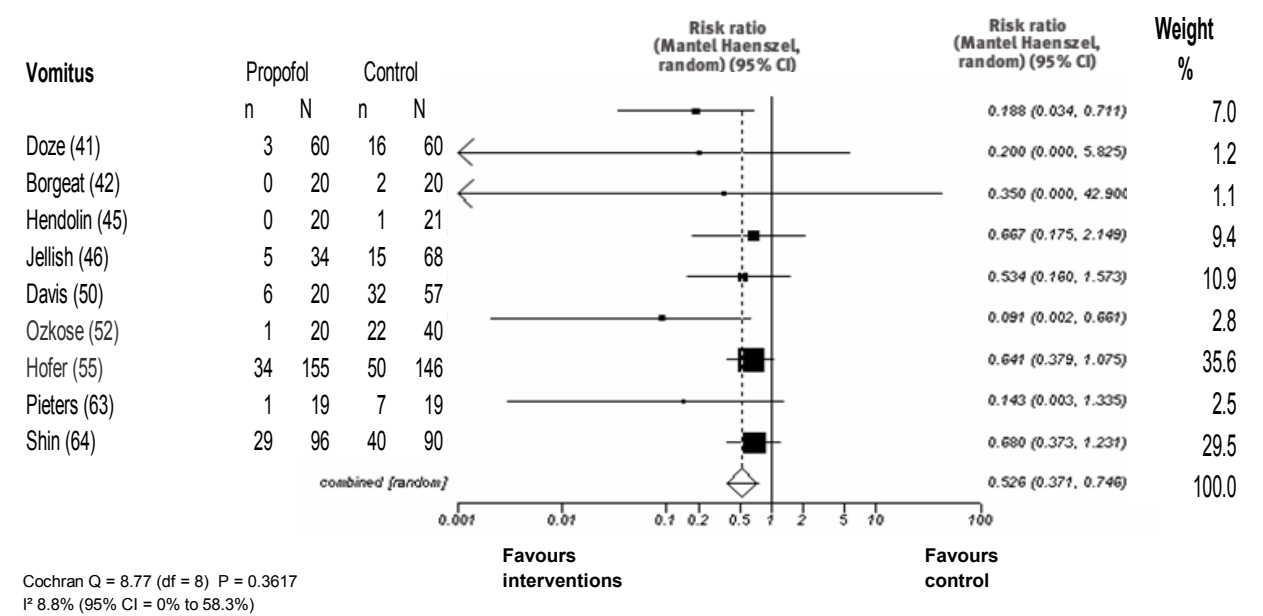
Fig. 5. Risk of postoperative vomiting after propofol anesthesia.

The presence of vomiting was analyzed in 9 researches. The risk ratio for vomiting was RR= 0.526 (95% CI 0.371-0.746) in intervention group with propofol (Fig. 5).
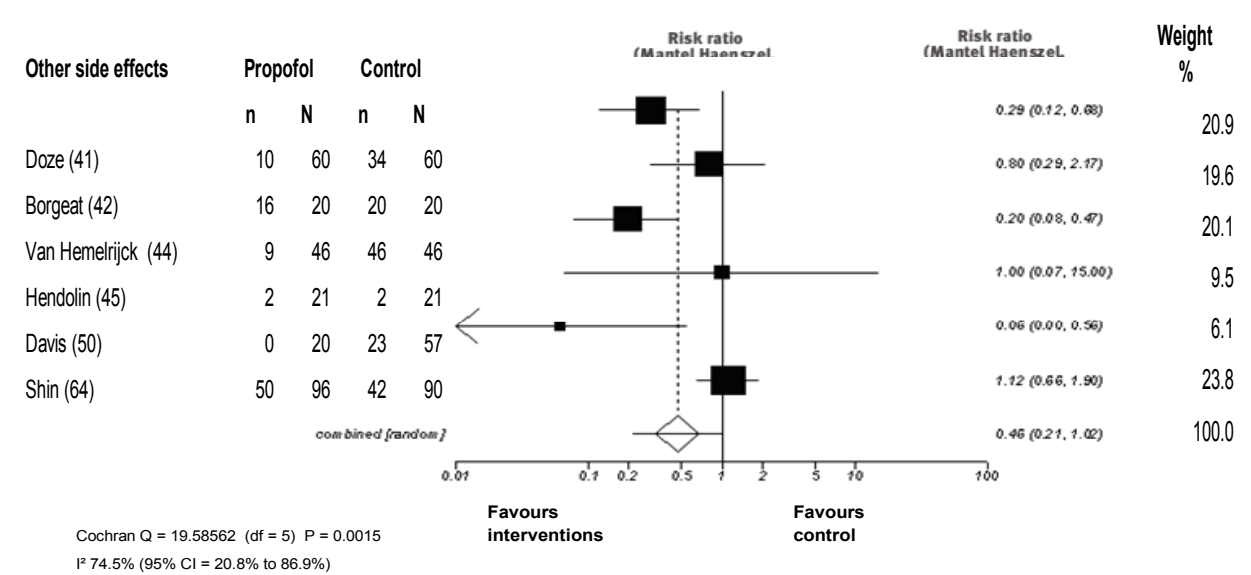
Fig. 6. Risk of the other side effects after propofol anesthesia during the postoperative period.

The other side effects which occurred in patients anesthetized with propofol were analyzed in 9 researches. In the term "the other side effects" was included: pain during propofol injection in induction period, bradycardia, hypotension, and spontaneous movements also described in perioperative period. Apnea, hypersalivation, laryngospasm and bronchospasm are also included in possible complications in postoperative period. The other side effects were also rare in the propofol anesthesia treated patients with the risk ratio 0.46 in intervention group (95% CI 0.21 to 1.02) (Fig. 6).

6. Discussion

Is propofol analgesic? ; still remain unclear. Experts held very different opinions on the value and clinical utility of an analgesic effect of propofol. The answers for this question were evaluated with pro *versus* con debates.

PRO: Propofol has analgesic effect

Discussions about analgesic effect of propofol restarted with the study published in *Anesthesia & Analgesia* in January 2008 by Cheng et al. The trial was based in hypothesis that women scheduled for hysterectomy or myomectomy and anesthetized with volatile anesthesia, isoflurane induces a hyperalgesic state, and that patients anesthetized with propofol was neutral in its modulation of pain sensitivity. They found that patients anesthetized with isoflurane reported more postoperative pain than those anesthetized with propofol. The other finding was the difference in postoperative opioid use with more requirements in those anesthetized with isoflurane.

Two years later, in 2010 issue of *Anesthesia & Analgesia*, Tan et al. report on a trial that tests the hypothesis that patients undergoing day surgery anesthetized with propofol have less pain and a better quality of recovery compared with patients anesthetized with sevoflurane. In this prospective, double-blind, randomized trial, the authors used a study design in

which one group had an induction with inhalation of sevoflurane followed by sevoflurane maintenance, whereas the other group had an IV induction with propofol followed by propofol maintenance. The subjects were treated during surgery with alfentanil, paracetamol, and diclofenac for pain and dexamethasone and ondansetron for nausea. Pain was treated after surgery using morphine until visual analog scale score was <4 and then oral oxycodone. The authors found that propofol provided a statistically significant (*P* < 0.01) difference, decrease in postoperative pain. Hendolin et al., 1994, found that propofol significantly reduced pain in the second hour compared with patients receiving isoflurane, corroborating the results of the present study.

The other study published in *Anesthesiology* August 2010 by Bandschapp et al., investigated the pain perception or central sensitization effects of propofol and its solvent (10% Intralipid) in healthy volunteers. They experienced decreased pain, hyperalgesia and allodynia elicited by intra-cutaneous electrical stimulation when they received a target-control infusion of propofol (2μg/ml) compared with controls (the solvent 10% Intralipid and saline). However, the results provide no evidence for a modulatory role of the solvent of propofol (10% Intralipid) in the analgesic and antihyperalgesic properties of propofol.

Propofol reduced pain by 40% and nearly abolished hypersensitivity which disappears on discontinuation of the drug. The EC_{50} for the analgesic effect of propofol was 3.2 μg/ml.

There is animal literature that addresses the modulatory effects of anesthetics in different nociceptive models.

In the 1990s, Ewen et al., found that in rats an IV infusion of propofol resulted in an initial decline followed by a rise in nociceptive threshold as the plasma concentration and degree of sedation increased. They suggest that smaller concentrations of propofol than sedative doses are responsible for hyperalgesia. However, the similar experiments in a postoperative pain models in mice were unable to detect any hyperalgesic phase at lower than sedative doses of propofol or on emergence (Udesky et al., 2005). Other groups have found an analgesic response to propofol, particularly in inflammatory pain models (Daniels&Roberts, 1998). A study in rodents by Guindon et al., 2007, demonstrated that in a test of inflammatory pain, locally injected propofol decreased pain behavior in a dose-dependent manner. The authors hypothesized that this antinociceptive activity was mediated, in part, by cannabinoid receptors 1 and 2 (CB1 and CB2). Gilron et al., 1999, however, showed that propofol suppressed hindpaw formalin-evoked expression of fos-like immunoreactivity (FLI) in spinal neurons, suggesting an important analgesic effect.

Clearly, most of the animal and human data on nociceptive effects mediated by propofol may provide advantages.

CON: **Propofol has not analgesic effect**

On the other hand, many studies with propofol in both animals and humans have failed to demonstrate any evidence of analgesic-like activity.

In an animal study by Merrill et al., 2006, propofol produced anesthesia but failed to produce the experimental findings typically associated with nociception, suggesting that propofol lacks analgesic properties. Accurately, propofol sufficient to produce immobility did not prevent increased activation (c-fos expression) of spinal neurons by intraplantar formalin injection, a finding consistent with propofol lacking analgesic properties. Mice with a mutation of the gamma-aminobutyric acid type A receptor were resistant to propofol anesthesia, supporting the importance of this receptor for propofol's action. Another rodent study (Ng & Antognini, 2006) found that isoflurane and propofol both had similar effects on

neuronal "windup" in the spinal cord, a factor associated with persistent pain. The study from Goto et al., 1994, reported that propofol, unlike pentobarbital, had no effect on second-phase nocifensive behavioral responses elicited by formalin injection in the hind paws of rats. Wilder-Smith et al. , 1995, also determined that propofol infusions did not affect thermal pain thresholds.

The human studies of interest, (Boccara et al., 1998) compared postoperative pain and analgesic requirements in patients receiving propofol or isoflurane for maintenance of anesthesia and reported that patients receiving propofol actually had increased pain and opioid requirements for the first 6 hours after surgery compared with patients receiving isoflurane. These findings were exactly the opposite of the findings of Cheng et al.

We conduct a more recent clinical study, published in *Anesthesia & Analgesia* in November 2008, by Fassoulaki et al., in patients undergoing abdominal hysterectomy or myomectomy under sevoflurane, desflurane or propofol anesthesia. Anesthesia was induced with propofol, morphine and cisatracrium; and maintained with sevoflurane or desflurane or propofol. Postoperative analgesia was maintained with morphine. They were unable to demonstrate any difference in postoperative pain scores or in the requirement for opioid analgesic medication among patients maintained with propofol, sevoflurane, or desflurane.

Presented data explained the inconsistency between the studies regarding the post-operative analgesic effect of propofol.

Our findings support the analgesic effect of propofol.

Postoperative nausea and vomiting (PONV) are unpleasant, often underestimated side effects of anesthesia and surgery, not devoid of medical complications. Prevention with antiemetics is only partially effective. Propofol has been shown recently to possess antiemetic properties in several situations.

The limitation of our analysis is mainly related to the methodological heterogeneity of several studies. The dose of propofol varied between the studies and my influenced the postoperative analgesic effect. The methods of postoperative pain assessment my bias the results of our meta-analyses. On the other hand, the number of analyzed clinical trials may also bias our results.

7. Conclusions

Our meta-analysis indicates that propofol provides a prolonged and improved postoperative analgesia with few adverse effects compared with an other inhalation and intravenous anaesthetics. However, propofol have improved antiemetic effect. The other side effects are minimal, with exception of pain during injection of propofol.

Propofol changed the practice of anesthesia, nevertheless postoperative analgesia with ordinary analgesics must be sustained.

Finally, we accomplished that propofol is not an analgesic, but many studies have certainly demonstrated analgesic properties of propofol.

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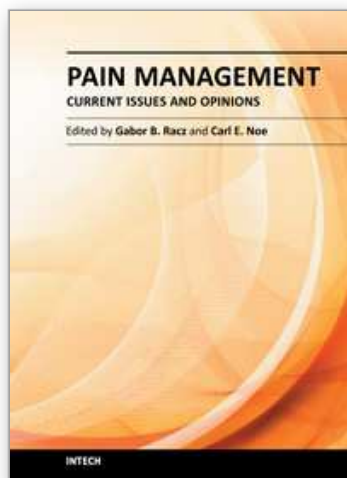
Pain Management - Current Issues and Opinions
Edited by Dr. Gabor Racz

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