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Original Contribution

Hypnotic agents for induction of general anesthesia in cesarean section patients: A systematic review and meta-analysis of randomized controlled trials☆

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ABSTRACT

Study objective: An ideal induction drug for cesarean section (CS) must have quick action, with minimum side effects such as awareness, hemodynamic compromise, and neonatal depression. Thiopentone is frequently used; however, no reliable evidence is available to support its use as a dedicated hypnotic agent in this setting.
Design: A systematic review and meta-analysis, using PRISMA methodology, of randomized controlled trials (RCTs), comparing women undergoing CS using thiopentone with those undergoing CS with propofol, ketamine, or benzodiazepines as hypnotic agents.
Data sources: Comprehensive search without language restrictions of MEDLINE, EMBASE, and the Cochrane Controlled Trials Registers until May 2015, with an update in January 2017. Included trials must have reported at least one of the following variables: neonatal arterial or venous umbilical blood gas, maternal systolic blood pressure pre- and post-intubation, or Apgar score.
Main results: A total of 911 patients from 18 RCTs were eligible for quantitative analysis. The increase in maternal systolic blood pressure was smaller in patients administered propofol, compared with those administered thiopentone (weighted mean difference [WMD]: −11.52 [−17.60, −5.45]; $p = 0.0002$). Induction with propofol also resulted in a significantly lower umbilical arterial pO_2 (WMD: −0.12 [−0.20, −0.04]; $p = 0.004$) than induction with thiopentone. A comparison between propofol and thiopentone revealed no significant differences in other umbilical blood gas parameters or in Apgar scores. In contrast, when comparing ketamine with thiopentone, the number of neonates with a lower Apgar score (< 7) at 1 and 5 min was significantly higher in the ketamine group than in the thiopentone group ($p = 0.004$).
Conclusion: The evidence, based on sparse and relatively old trials, indicates that propofol and thiopentone are equally suited for CS. After 1 and 5 min, ketamine yields lower Apgar scores than thiopentone. Additional well-designed trials are needed to reach firmer conclusions.

1. Introduction

Various induction agents are used when performing cesarean section (CS) under general anesthesia. Since 1934, thiopentone has often been the drug of choice, despite its rapid placental transfer and barbiturate-related cardiorespiratory depressive effects. Drug-induced hypotension may reduce blood flow to the placenta, endangering the fetus [1–3]. The degree of transfer depends on the pharmacodynamic profile of the drug, as well as factors related to utero-placental circulation and the fetal unit [4]. Therefore, the ideal induction agent should rapidly induce unconsciousness and provide a good recovery profile, in combination with minimal direct or indirect neonatal depression [5].

There are a number of agents that might be suitable for use in the induction of general anesthesia in cesarean section patients, in place of thiopentone. Alternative agents might include benzodiazepines, ketamine, and propofol. However, as in the case of thiopentone, these agents all exhibit high degrees of lipid solubility and rapid maternal-fetal equilibration.

While midazolam, a relatively short-acting, water-soluble imidazobenzodiazepine, may reduce the frequency of awareness [5,6] the use

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of ketamine may cause dysphoria; thus, it has resulted in concerns regarding intraoperative awareness [7]. Currently, propofol is widely used in both surgery and the intensive care ward [8], primarily because of its rapid metabolism and excretion [9]. Propofol is currently the standard agent for the induction of anesthesia in most institutions; consequently, some authors have questioned future usage of thiopentone in obstetric anesthesia [10,11]. However, no reliable evidence is currently available to support the use of one specific drug as a dedicated hypnotic agent in this setting.

Therefore, the aim of this systematic review was to compare the efficacy and safety profiles of propofol, ketamine, and benzodiazepines with those of thiopentone, as induction agents in women receiving general anesthesia for CS, to identify an "evidence-supported" practice.

2. Materials and methods

2.1. Search strategy

This meta-analysis was performed and reported according to the PRISMA guidelines [13]. A systematic literature search was performed without language restrictions in MEDLINE, EMBASE, and the Cochrane Controlled Trials Registers, using the keywords "cesarean section" in combination with "propofol," "thiopentone," "ketamine," "etomidate," and "benzodiazepine." "Thiopentone" and comparable compounds (e.g., "thiamylal") were included. Electronic searches were conducted until May 2015, and bibliographies of the retrieved articles and reviews were also screened. An updated search in January 2017 did not reveal any new eligible articles.

2.2. Inclusion criteria

Published full reports of randomized controlled trials were considered for inclusion if the study population consisted of women undergoing CS with general anesthesia, where at least one of the following induction agents was used: thiopentone, propofol, ketamine, or benzodiazepine. We did not include treatments that tested a combination of induction agents. At least one of the following primary outcome variables was required to be reported: arterial or venous umbilical blood gas (UBG; pH, pO_2, pCO_2, and base excess), or Apgar score. Awareness and maternal systolic blood pressure (SBP) were included as additional outcomes.

2.3. Data extraction and quality assessment

After completing the initial search, two authors (JUS and KHK) screened the retrieved reports for inclusion, based on the available abstracts. Reports that did not meet the inclusion criteria were discarded from analysis at this stage. Furthermore, reports that met the inclusion criteria, based on the retrieved full-text versions, were first independently scored by two authors (KHK and JUS) using the 5-point Oxford scale, which assesses the quality of randomization, blinding, withdrawals, and dropouts [12]. Only randomized trials were considered. An additional risk-of-bias scoring, using the Cochrane Risk of Bias tool, was performed in a second step. Scoring disagreements were resolved by discussion. Treatments that were tested in only two or fewer trials were excluded from the quantitative analysis to avoid a disproportionate distribution of weight.

2.4. Statistical analysis

We used a random effects model for data analysis, assuming that heterogeneity existed among the analyzed patient populations, interventions, and clinical settings. Heterogeneity was estimated using Cochrane's Q and I^2 measures; it was further evaluated through sensitivity analysis by stepwise exclusion of every individual study included in the meta-analysis. UBG and maternal SBP were analyzed using weighed mean difference (WMD; according to the inverse of the reported variance), including 95% confidence intervals (CIs). Apgar scores < 7 at 1 and 5 min after delivery were analyzed using odds ratios (ORs), including 95% CI. The data were analyzed using Review Manager, version 5.3.5 (Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). Additional trial sequential analysis (TSA), via TSA viewer software (version 0.9 beta, Copenhagen Trial Unit, Copenhagen, Denmark), was performed if a risk of random error was indicated. TSA was performed with standardized assumptions (Type I error: 5%, power: 80%, model variance-based heterogeneity correction, empirically calculated MD and variance). Additional summary-of-findings tables were created using GRADEpro GDT (GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 [developed by Evidence Prime, Inc.], available from gradepro.org). These tables are available as supplementary data.

3. Results

3.1. Study selection

The initial search yielded 1119 results. A total of 1054 publications were excluded at this stage for various reasons (Fig. 1). The remaining 65 potentially relevant publications were further analyzed. Finally, data from 18 trials published between 1985 and 2015, including a total of 911 patients, were eligible for quantitative analysis.

3.2. Characteristics of included studies

For quantitative analysis (Table 1), only trials that compared thiopentone with propofol [3,5,8,9,14–22] or ketamine [7,23–26] were included (Table 1). Anesthesia was maintained with several volatiles, including propofol in some cases. In the thiopentone versus ketamine group, Baraka et al. used either 50% nitrous oxide and 0.5% halothane in oxygen (groups I and III) or 1% halothane in oxygen (groups II and IV) for maintenance. [23] For analysis, we divided this group into Baraka I (groups I and III) and Baraka II (groups II and IV). Krissel et al. randomly divided their study population into three groups [24]. Anesthesia was induced with thiopentone ($4\,mg\,kg^{-1}$), ketamine ($1\,mg\,kg^{-1}$), or a combination of both agents. Data from the first two groups were used for quantitative analysis. In the thiopentone group, anesthesia was maintained with a nitrous oxide/oxygen mixture with 0.8% enflurane after induction, and with 100% oxygen plus 0.4% enflurane shortly before the uterine incision, continuing until delivery. In the ketamine group, anesthesia was maintained in the same manner, except that enflurane was not used. In its place, an additional bolus of $0.25\,mg\,kg^{-1}$ of ketamine was administered, if required [24]. The results for the remaining agents could not be analyzed quantitatively because an insufficient number of trials met the inclusion criteria.

The median number of patients among all trials was 41 per study (range 20–150). Few trials reporting on awareness used uniform outcome parameters; therefore, the data on awareness are discussed in a qualitative manner. The median quality score of the included trials was estimated to be as low as 2 (range 1–5; Table 1). The risk-of-bias assessment with the Cochrane tool found uncertainty regarding randomization and allocation in most included trials, which corresponded to an increased risk of bias (Fig. 2a, b).

3.3. Quantitative analysis of studies comparing thiopentone with propofol

Thirteen randomized trials, consisting of 694 patients, compared thiopentone with propofol (Table 1) [3,5,8,9,14–22]. The data were sufficient to allow the following comparisons: umbilical venous and arterial pO_2, pCO_2, umbilical venous base excess, maternal systolic blood pressure (pre- and post-intubation), and Apgar score at 1 and 5 min after delivery.