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EFFICACY AND SAFETY OF PROPOFOL AS COMPARE TO OTHER ANESTHETICS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction

Propofol is used in most of surgical, endoscopic and colonoscopy procedures which commonly requires general anesthesia, and propofol is one of the most widely used intravenous anesthetics. Propofol is known to have many advantages over other anesthetic agents, including rapid induction of anesthesia, early recovery, and fewer complications such as postoperative nausea and vomiting.[1]

It is a safe and effective intravenously administered is a short-acting sedative hypnotic drug with weak amnesic property sedative agent with a rapid onset of action and fast recovery time.[2] It has been used extensively as an anaesthetic agent, particularly in procedures of short duration. [3]More recently it has been investigated as a sedative in the intensive care unit (lCU) where it produces sedation and hypnosis in a dose-dependent manner.[4] Over the course of the past three decades, the use of propofol has evolved from use as a hypnotic agent, to use as an ultra-short acting sedative agent for induction and maintenance of anesthesia in monitored anesthesia care (MAC), to non-anesthesiologist-administered propofol (NAAP) in different surgical procedures.[5] The extensive use of propofol is hindered both by the agent's safety profile (risk of deep sedation leading to respiratory depression to the extent of apnea, with no known antagonists/ reversal agents) and by the US Food and Drug Administration (FDA) package labeling stating that propofol "should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure".[6] In an attempt to alter the package labeling of propofol, a petition was submitted to the FDA by the American College of Gastroenterology (ACG). That petition was denied by the FDA in 2010, on the grounds that the ACG failed to demonstrate an adequate safety profile of propofol to support their petition.[7] Noncomparative and comparative trials have evaluated the use of propofol for the sedation of mechanically ventilated patients in the leu (postsurgical, general medical, trauma). Overall, propofol provides satisfactory sedation and is associated with good haemodynamic stability.[8] Patients sedated with propofol also tend to have a faster recovery (time to spontaneous ventilation or extubation) than patients sedated with other anaesthetics.[9] While experience with propofol for the sedation of patients in the lCU is extensive, there are still areas requiring further investigation.[10] Data from a limited number of studies assessing the efficacy of propofol for the sedation of patients following head trauma indicate that propofol provides adequate sedation and control of cerebral haemodynamics.[11] As there is much contradicting results and trials found in literature about the efficacy and safety of propofol as compare to other anesthetics. Therefore, A systematic review and meta-analysis are being undertaken to evaluate the efficacy and safety of propofol compared to other anesthetics to ascertain the current areas that warrant further exploration.

Materials and Methods:

This systematic review is prepared in accordance with the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).[12]

The inclusion and exclusion criteria for the studies to be included in this systematic review are:

Inclusive Criteria:

Study Type.

included randomized controlled trials (RCTs) related to the efficacy and safety of propofol as compare to other anesthetics. Studies enrolled were reported in English.

Study Subject.

Adult subjects age above eightenn years undergoing any surgical procedure which is using propofol and anesthetic agent.

Adults of either gender or any age were considered eligible.

Intervention.

The intervention in the control group is any anesthetic, whereas the treatment group received propofol.

Outcome.

mean duration of sedation ,adverse events and complications after intervention.

Exclusion Criteria

The exclusion criteria are duplicate articles; non interventional studies, such as case-control study, cohort study, cross-sectional study, case reports and experiences, theory research, and reviews; nonclinical trials, such as animal testing;

- ***Quality Assessment.*** The quality of all trials is evaluated independently by two researchers, using the Cochrane collaboration's tool for bias risk assessment.[13] The following items are assessed: random sequence generation, allocation

concealment mechanism, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The outcomes are evaluated as high risk, unclear, and low risk. Unclear will be assigned if we could not find any descriptions of the item, low risk is assigned if the information is sufficient, and high risk is assigned if the information is inadequate. The risk of bias assessment and risk of bias summary is shown in figure 7 and 8.

- **Search Methods for identification of studies**
- ***Electronic searches***

Detailed search strategies for each electronic database were developed. These were based on the one used for Pubmed (Ovid) Medline, and (Ovid) Embase but with appropriate database related search strategy modification such as the use of truncations, wildcards, and filters. The search strategy for Medline (Ovid) was combine subject search with the Cochrane Highly sensitive search strategy filter for randomised controlled trials as published. [13]. We avoided the use of the Cochrane highly "sensitive and specific" RCT search filter unless the amount of retrieved data is deemed too large using the highly sensitive filter.[13]

The subject search used a combination of the controlled vocabulary terms "Mesh terms" and free-text words based on the search strategy developed for Medline.

We will search the following databases with English language restriction applied in each database until January 2021

- Medline (Ovid)
- Embase (Ovid)
- PubMed
- Cochrane Central Register of controlled Trials (CENTRAL) in the Cochrane library (current issue)

Searching other resources

We checked the references of all the included studies and use the citation alert to search for more up to date publications or new studies.

Statistical Analysis.

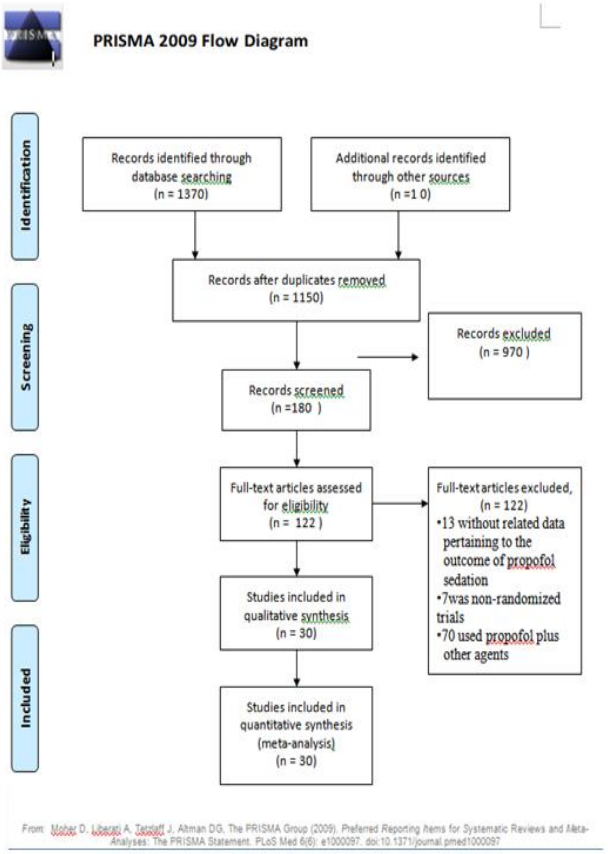
Data Extraction and Synthesis. The initial screens for eligibility of retrieved articles were performed based on the title and abstracts and duplicates were removed. The remaining eligible articles considered for inclusion was reviewed by two review authors (AS, FC) independently using pre-specified inclusion and exclusion criteria. Disagreement between reviewers was resolved through discussion with other review authors (KM, Sk, Hk,). The flow of information through the review was illustrated within a PRISMA flow diagram (Figure 1) in our full systematic review and meta-analysis report, as recommended by the Cochrane Handbook [13]. Pertinent dichotomous data were extracted and entered in the Review Manager 5.4 software for analysis. The risk ratio (RR) and (OR) is used for dichotomous data, whereas the mean difference (MD) and standard deviations (SDs) are applied for continuous variables; for both, the corresponding 95%CI and forest plots were used. SD values are used when the data are in the same unit; and conversion should be made when different units are encountered in this systematic review and meta-analysis. Heterogeneity across individual studies was assessed using the $\chi 2$ test for the Cochrane Q statistic and I^2.[13]

An I^2 value > 60% or a $\chi 2$ P value < 0.1 was considered to indicate substantial statistical heterogeneity between studies. Visual inspection of funnel plots was conducted to assess potential publication bias.

Results

Description of included studies

The initial search strategy yielded 1,252 potentially relevant articles. After screening the titles and abstracts, 970 records were excluded, and the remaining 180 articles were retrieved for the final determination of eligibility. After we reviewed the full texts of 122 potentially relevant articles and reference lists, 30 articles were included in the meta-analysis. The flow diagram of literature search according to PRISMA guidelines is show in below figure 1.[12]



THE BASELINE characteristics of the thirty RCTs included in the meta-analysis are summarized in Table 1. These studies were published between 1990 and 2018 and a total of 2,244 patients were investigated, 1256 of whom received propofol as sedative and 988 of whom received different sedatives according to the studies.

Table 1:

Study ID	Country	Sedative	No. of patients	Gender	Mean Age
Patterson et al 1991	Ireland	Propofol/Fentanil	40	Male/Female	56.2
Kostash et al 1994	Canada	Propofol/Medazolam	19	Male/Female	55.7
Carlsson et al 1995	Sweden	Propofol/Medazolam	45	Male/Female	56.4
Izquierdo-Riera et al 1998	Spain	Propofol/Medazolam	67	Male/Female	53.5
Werhmann et al 19999	Germany	Propofol/Medazolam	99	Male/Female	54.7
Koshy et al 2000	USA	Propofol/Medazolam	150	Male/Female	59.1
Krugliak et al 2000	Israel	Propofol/Medazolam	27	Male/Female	52.8
Camps et al 2000	Spain	Propofol/Sufentanil	63	Male/Female	48.4
Ju-Mei et al 2001	Singapore	Propofol/Alfentanil	44	Male/Female	58.1
Sipe et al 2002	USA	Propofol/Medazolam	40	Male/Female	60.1
Moerman et al 2003	Belgium	Propofol/Medazolam	40	Male/Female	56.3
Gasparovic et al 2003	Croatia	Propofol/Medazolam	125	Male/Female	59.3
Weston et al 2003	USA	Propofol/ketamine	20	Male/Female	53.7
Ulmer et al 2003	USA	Propofol/Meperidine	125	Male/Female	57.2
Vargo et al 2004	USA	Propofol/Medazolam	38	Male/Female	60.6
Ghori et al 2007	Ireland	Propofol/Medazolam	25	Male/Female	52.3
Mandel et al 2008	USA	Propofol/Remifentanil	50	Male/Female	45.8
Riphaus et al 2009	Germany	Propofol/Medazolam	96	Male/Female	52.9
Correia et al 2011	Brasil	Propofol/ketamine	145	Male/Female	62.7
Khamaysi et al 2011	Israel	Propofol/Medazolam	60	Male/Female	49.8
Tanguy et al 2012	France	Propofol/Medazolam	29	Male/Female	57.4
Agrawal et al 2012	India	Propofol/Medazolam	82	Male/Female	60.1
Bastaki et al 2013	Greece	Propofol/Medazolam	35	Male/Female	56.4
Fanti et al 2015	Italy	Propofol/Medazolam	60	Male/Female	61.1
Eberl et al 2014	Netherlands	Propofol/Remifentanil	60	Male/Female	54
Schroeder et al 2016	USA	PropofolMidazolem	126	Male/Female	58.6
Padmanabhan et al 2017	USA	Propofol/Fentanil	300	Male/Female	61.4
Ferreira et al 2016	Portugal	Propofol/Remifentanil	287	Male/Female	58.6
Liu et al 2009	China	Propofol/Alfentanil	178	Male/Female	55.3
Külling et al 2005	Switzerland	Propofol/meperidine	100	Male/Female	48.1

Four of the studies involved brain injury [14-16]. Patients were of similar ages generally in their late forties. The studies reported by Camps et al,Ghori et al, Tanguy et al and Riera et al included a variety of severe brain trauma patients, including patients with severe TBI[15]. Whereas Tanguy et al reported only patients with severe traumatic brain injury in their study[17]. Further six studies were included which reported procedural sedation for any non-elective painful procedures in emergency department.[14,18-22] "Painful procedures" included orthopedic manipulation (e.g., reduction of a fracture or dislocation), electrical cardio version, abscess drainage, burn-dressing changes, wound debridement, suturing of lacerations, or foreign body removal. Nine studies reported the use of propofol for colonoscopy procedures [23-31].

SYNTHESIS OF RESULTS

Procedure duration: Overall statistical analysis of studies with a total of 2244 patients reported procedure time. Which showed no statistical difference was found between the propofol and other sedative groups OR 0.92; 95% CI 0.81, 1.06; P, 0.01); x^2 and I^2 were 0.15 (P=0.86) and 0.1%, respectively, indicating the absence of heterogeneity among the studies. (Figure 2).

Subgroup analysis indicated that propofol provided significantly better sedation than traditional sedative agents for Brain trauma (OR 0.84; 95% CI 0.50, 1.42; P=0.0001) and colonoscopy (OR 0.92; 95% CI 0.70, 1.20; P=0.56), there was not a significant discrepancy calculated for upper gastrointestinal endoscopy (OR 0.96; 95% CI 0.80, 1.15; P=0.69). The x^2 and I^2 were respectively 2.38 (P = 0.64) and 0% for brain trauma injury, 0.17 (P = 0.31) and 0% for colonoscopy, and 1.11 (P = 0.56) and0% for upper gastrointestinal endoscopy, indicating the absence of heterogeneity among the studies (Figure 2).

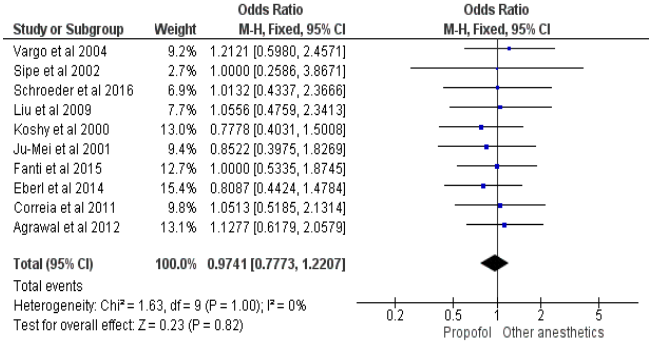


Figure 3.Forest plot for PARS

Post-anesthesia recovery score (PARS).

Ten studies provided data on recovery time, all of them found a higher PARS in the PS group than in the TS group (0.97;95% CI 0.77, 1.22; P,0.01). The chi^2 and I^2 were 1.63 (P=0.82)

and 0.0%, respectively, suggesting no heterogeneity among the studies.(figure 3).

Sedation level.

The level of sedation was correctly cleared as the lack of patient opposition to the certain procedure. Eight studies provided data on sedation level. Propofol administration extensively improved the sedation level as compared to other traditional sedative agents for different procedures (OR 0.96; 95% CI 0.75, 1.23; P, 0.01); chi^2 and I^2 were 0.33 (P=0.77) and 0.1%, respectively, indicating the absence of heterogeneity among the studies (Figure 4). Subgroup analysis indicated that propofol provided significantly better sedation than traditional sedative agents for Brain trauma (OR 0.84; 95% CI 0.50, 1.42; P=0.0001) and colonoscopy (OR 0.92; 95% CI 0.70, 1.20; P=0.56), there was not a significant discrepancy calculated for upper gastrointestinal endoscopy (OR 0.96; 95% CI 0.80, 1.15; P=0.69). The x^2 and I^2 were respectively 2.38 (P = 0.64) and 0% for brain trauma injury, 0.17 (P = 0.31) and 0% for colonoscopy, and 1.11 (P = 0.56) and0% for upper gastrointestinal endoscopy, indicating the absence of heterogeneity among the studies (Figure 2).

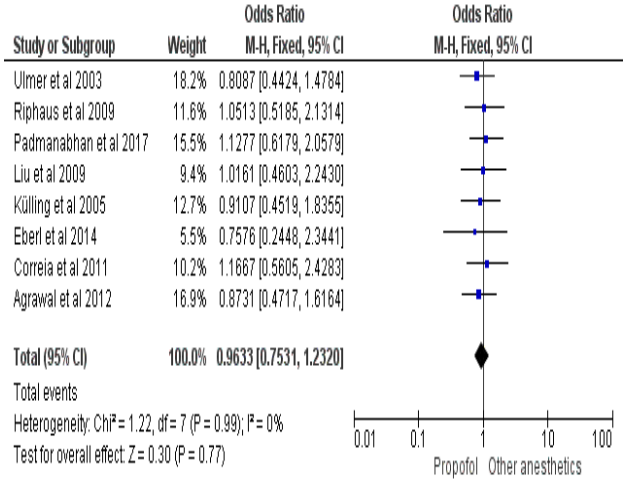


Figure 4.Forest plot sedation level

Recovery duration:

On recovery duration total eleven studies provided quantitative data for statistical analysis. Propofol sedation considerably reduced mean recovery time compared with other traditional sedations for all procedures combined (0.96; 95% CI –0.78, –1.19; P, 0.10). The chi^2 and I^2 were 1.66 (P, 0.77) and 0%, respectively, indicating no heterogeneity among the studies.(figure 5)

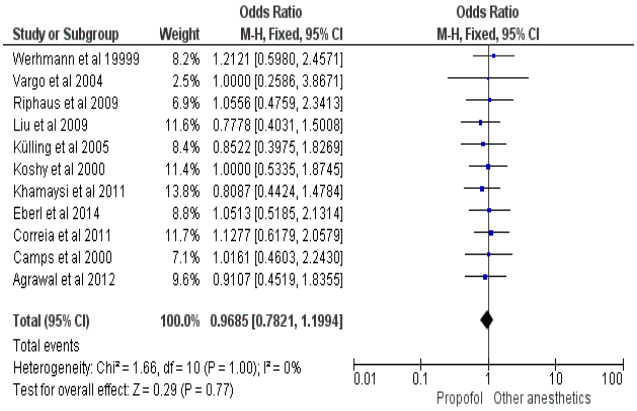


Figure 5: Forest plot for recovery time

Patient satisfaction.

We collected data from thirteen studies on patient satisfaction. Pooling the results for propofol and control groups revealed no significant difference in patient satisfaction (OR 0.96; 95% CI 0.79, 1.17; P=0.74). The chi^2 and I^2 were 1.67 (P=1.00) and 0%, respectively, suggesting no heterogeneity among the studies (Fig. 6).

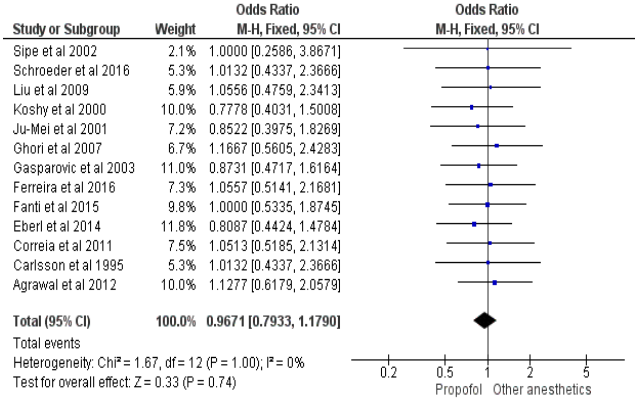


Figure 6: Funnel showing results for Patient satisfaction.

Publication Bias

To assess the publication bias among the studies Funnel plot and Egger's testing were performed. Funnel plot analysis is displayed in figure 9, for all included studies which appeared appeared to be symmetrical.

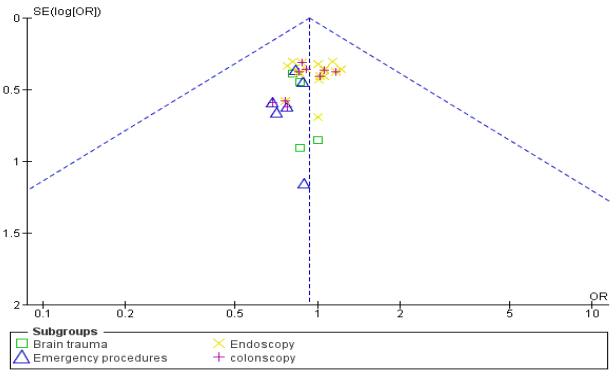


Figure 9: Funnel plot of all included studies

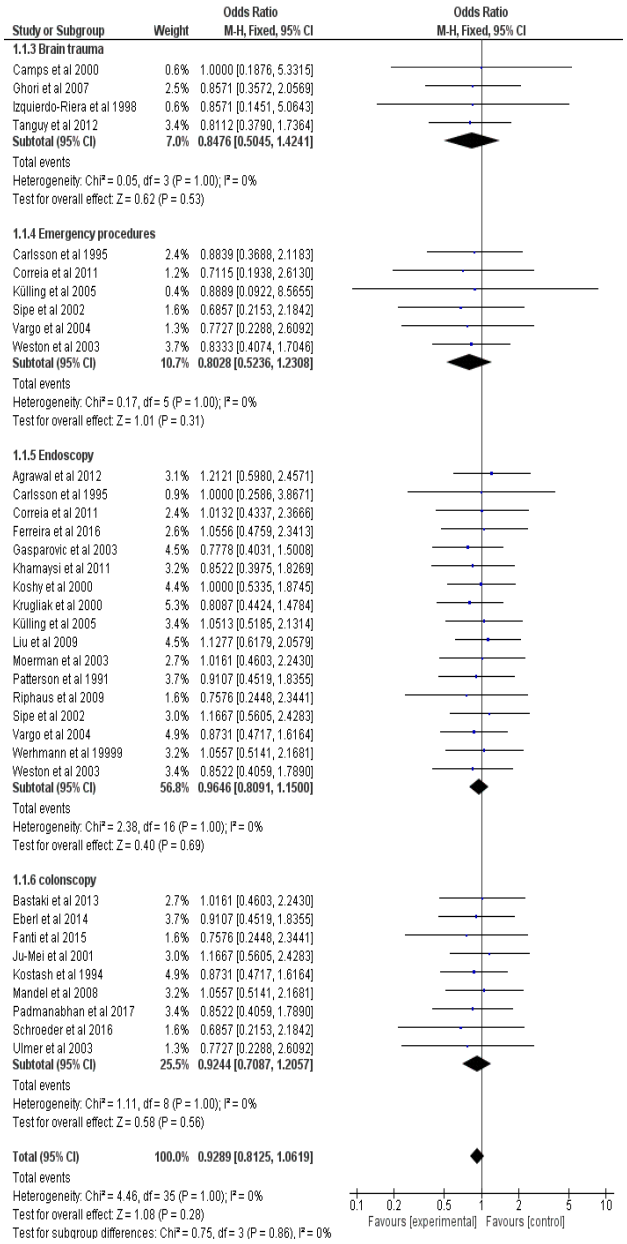


Figure 2: Forest plot showing results for Procedure duration

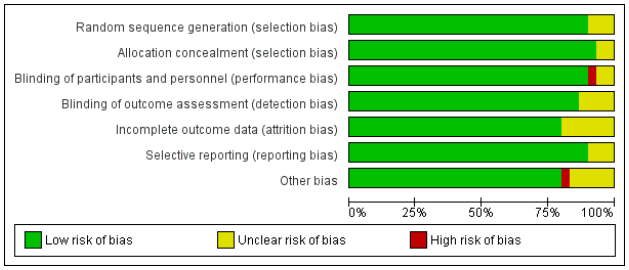


Figure 7: RISK OF BIAS GRAPH

DISCUSSION:

This systematic review and meta-analysis combines the results of thirty included studies and 2244 patients to compare safety and efficiency outcomes of propofol with other traditional sedatives in multiple different procedures in diverse setting of hospital. There were not any statistically significant differences in all outcomes between sedative agents. Our assessment of satisfaction and efficiency outcomes found insignificant benefits to the use of propofol. Patient satisfaction was higher with propofol; nonetheless, differences within studies were seldom small. Patients sedated with propofol had related procedure times as those sedated with midazolam .We found decreases in recovery and discharge duration when propofol was used; nevertheless, the unconditional differences in time saved varied considerably across studies and were often negligible, with the largest study reporting a difference of thirty seconds. The results of this study are mostly in agreement with previously carried systematic reviews meta-analyses that compare propofol with traditional sedatives in certain procedures. Just like those other studies, we didn't conclude a significant difference in procedure time with the use of propofol.[32,33] a result that we were not capable to reproduce might have associated with those studies inclusion of different several different sedatives in the conventional sedative list. If sedative agents excluding midazolam were related to high rates of cardio respiratory proceedings, the addition in the traditional sedative group may have made propofol appear to be superior despite no difference between propofol and midazolam.

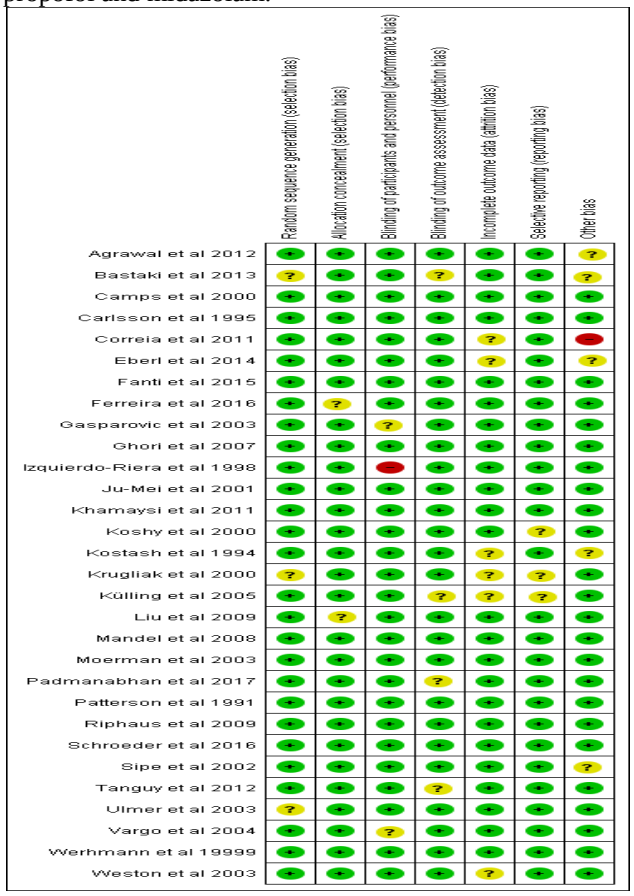


Figure 8: **RISK OF BIAS SUMMARY.**

Analgesics and intravenous sedation can be used either alone or in combination for a synergetic effect to comfortably perform the procedure while maintaining an adequate level of sedation. Sedation in endoscopy is safe when we correctly select, individualize, and optimize the medicine dosage for each type of patient. One of the primary considerations is patient comorbidites, including hepatic dysfunction which can lead to difficulty in clearance, recirculation, and increased half-life of drugs.[34] Recent multicenter cross-sectional study that included multiple endoscopic procedures in patients with cirrhosis found that adverse events were uncommon and cardiovascular adverse events were related to unhealthy patients and those requiring general anesthesia.[35] Different adverse events in the study were mainly seen in couple of included trials,[36-39] which included endoscopic therapeutic procedures esophageal varices management to be expected because of the prolonged procedure time and the need for higher sedation dose for patient ease and comfort. furthermore, the definitions of sedation and recovery time were varied among the studies. Gasprovic et al.[40] distinct the sedation duration as the time from first study medication until return to baseline mental status and recovery time as the time from procedure completion until return to baseline psychological status. Moerman et al.[41] reported sedation time as the time from first medication administration to time of procedure completion and recovery time as the interval from the last dose of medication administered until discharge criteria were met. [42]Paterson et al. showed sedation time as the first administration of study drug to first purposeful verbal response and recovery time as the time of last administration of study drug to first purposeful verbal response.[43]

In a nutshell, there is no evidence to suggest that the risk of complications after the use of propofol standout from that of a combination of other traditional sedative agents, narcotics/benzodiazepines. Compared with other agents, propofol appears to have lower complications for multiple different procedure either surgical or in emergency set up. Even though the frequency of overall complications seems to be lower with propofol, a concise clinical trial is required to exhibit the advantage and safe use of propofol for different procedures in surgical and emergency setup of hospital.

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