ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2019 December 16; 11(12): 548-595

Published by Baishideng Publishing Group Inc

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 11 Number 12 December 16, 2019

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World Journal of Gastrointestinal Endoscopy

Volume 11 Number 12 December 16, 2019

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RESPONSIBLE EDITORS FOR THIS ISSUE

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Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
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EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

EDITORIAL OFFICE
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PUBLICATION DATE
December 16, 2019

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World J Gastrointest Endosc 2019 December 16; 11(12): 573-588

DOI: 10.4253/wjge.v11.i12.573

ISSN 1948-5190 (online)

META-ANALYSIS

Propofol *vs* traditional sedatives for sedation in endoscopy: A systematic review and meta-analysis

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Author contributions: Delgado AAA contributed to the acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; de Moura DTH contributed to the analysis and interpretation of data, revising the article; Ribeiro IB contributed to the acquisition of data, drafting the article, revising the article, final approval; Bernardo WM contributed to the analysis and interpretation of data, drafting the article, final approval; Bazarbashi AN contributed to the revising, editing and drafting article, final approval; dos Santos MEL and de Moura EGH contributed to the analysis and interpretation of data, drafting the article, revising the article, final approval.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors revised the

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Abstract

BACKGROUND

Propofol is commonly used for sedation during endoscopic procedures. Data suggests its superiority to traditional sedatives used in endoscopy including benzodiazepines and opioids with more rapid onset of action and improved post-procedure recovery times for patients. However, Propofol requires administration by trained healthcare providers, has a narrow therapeutic index, lacks an antidote and increases risks of cardio-pulmonary complications.

AIM

To compare, through a systematic review of the literature and meta-analysis, sedation with propofol to traditional sedatives with or without propofol during endoscopic procedures.

METHODS

A literature search was performed using MEDLINE, Scopus, EMBASE, the Cochrane Library, Scopus, LILACS, BVS, Cochrane Central Register of Controlled Trials, and The Cumulative Index to Nursing and Allied Health Literature databases. The last search in the literature was performed on March, 2019 with no restriction regarding the idiom or the year of publication. Only randomized clinical trials with full texts published were included. We divided sedation

manuscript according to the PRISMA 2009 Checklist.

Manuscript source: Unsolicited manuscript

Received: May 6, 2019
Peer-review started: May 8, 2019
First decision: August 2, 2019
Revised: August 17, 2019
Accepted: September 11, 2019
Article in press: September 11, 2019
Published online: December 16, 2019

P-Reviewer: Lin OST, Maltz C
S-Editor: Wang JL
L-Editor: A
E-Editor: Liu JH

therapies to the following groups: (1) Propofol versus benzodiazepines and/or opiate sedatives; (2) Propofol versus Propofol with benzodiazepine and/or opioids; and (3) Propofol with adjunctive benzodiazepine and opioid versus benzodiazepine and opioid. The following outcomes were addressed: Adverse events, patient satisfaction with type of sedation, endoscopists satisfaction with sedation administered, dose of propofol administered and time to recovery post procedure. Meta-analysis was performed using RevMan5 software version 5.39.

RESULTS

A total of 23 clinical trials were included (n = 3854) from the initial search of 6410 articles. For Group I (Propofol *vs* benzodiazepine and/or opioids): The incidence of bradycardia was not statistically different between both sedation arms (RD: -0.01, 95%CI: −0.03–+0.01, I^2: 22%). In 10 studies, the incidence of hypotension was not statistically difference between sedation arms (RD: 0.01, 95%CI: −0.02–+0.04, I^2: 0%). Oxygen desaturation was higher in the propofol group but not statistically different between groups (RD: −0.03, 95%CI: −0.06–+0.00, I^2: 25%). Patients were more satisfied with their sedation in the benzodiazepine + opioid group compared to those with monotherapy propofol sedation (MD: +0.89, 95%CI: +0.62–+1.17, I^2: 39%). The recovery time after the procedure showed high heterogeneity even after outlier withdrawal, there was no statistical difference between both arms (MD: -15.15, 95%CI: −31.85–+1.56, I^2: 99%). For Group II (Propofol *vs* propofol with benzodiazepine and/or opioids): Bradycardia had a tendency to occur in the Propofol group with benzodiazepine and/or opioid-associated (RD: -0.08, 95%CI: −0.13–−0.02, I^2: 59%). There was no statistical difference in the incidence of bradycardia (RD: -0.00, 95%CI: −0.08–+0.08, I^2: 85%), desaturation (RD: −0.00, 95%CI: −0.03–+0.02, I^2: 44%) or recovery time (MD: -2.04, 95%CI: −6.96–+2.88, I^2: 97%) between sedation arms. The total dose of propofol was higher in the propofol group with benzodiazepine and/or opiates but with high heterogeneity. (MD: 70.36, 95%CI: +53.11–+87.60, I^2: 61%). For Group III (Propofol with benzodiazepine and opioid *vs* benzodiazepine and opioid): Bradycardia and hypotension was not statistically significant between groups (RD: -0.00, 95%CI: −0.002–+0.02, I^2: 3%; RD: 0.04, 95%CI: −0.05–+0.13, I^2: 77%). Desaturation was evaluated in two articles and was higher in the propofol + benzodiazepine + opioid group, but with high heterogeneity (RD: 0.15, 95%CI: 0.08–+0.22, I^2: 95%).

CONCLUSION

This meta-analysis suggests that the use of propofol alone or in combination with traditional adjunctive sedatives is safe and does not result in an increase in negative outcomes in patients undergoing endoscopic procedures.

Key words: Sedation; Digestive endoscopy; Propofol; Benzodiazepines; Opioids; Adverse events

Core tip: Propofol is commonly used for sedation during endoscopic procedures with increasing data suggesting its superiority to other sedatives, however with reported concerns about possible adverse events. This systematic review and meta-analysis discusses different variants of propofol-based sedation and how they compare to alternative sedatives such as those utilizing benzodiazepines and opioids. We demonstrate that the use of propofol, alone or in conjunction with alternative sedatives, is safe and carries no particular negative outcomes when compared to the widely available combination of alternative sedatives using in endoscopy.

Citation: Delgado AAA, de Moura DTH, Ribeiro IB, Bazarbashi AN, dos Santos MEL, Bernardo WM, de Moura EGH. Propofol *vs* traditional sedatives for sedation in endoscopy: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2019; 11(12): 573-588
URL: https://www.wjgnet.com/1948-5190/full/v11/i12/573.htm
DOI: https://dx.doi.org/10.4253/wjge.v11.i12.573

INTRODUCTION

In recent years, the use of propofol for sedation during endoscopy has been shown to be safe and effective. Propofol is associated with rapid onset of action and a short time to recovery of patient's cognitive functions post procedure[1-4]. Propofol may be administered alone or in combination with other sedative agents, such as benzodiazepines or opioids[5-7].

Sedation using propofol alone can be associated with risks and complications since it requires administration of larger doses to achieve an adequate level of sedation, which in turn can lead to dose-dependent adverse events[5,8]. Additionally, the isolated use of this drug has disadvantages related to its pharmacokinetic properties. Propofol can induce deep sedation, has no antidote for reversibility, has a narrow therapeutic index and causes adverse events including cardiopulmonary compromise requiring resuscitation[9,10].

However, previous studies have shown that the use of propofol as an adjunct to traditional sedatives such as benzodiazepines and opioids with moderate patient sedation is associated with lower risk of complications, improved patient cooperation and satisfaction, and shorter time to recovery post procedure[5,11].

Several studies have compared the use of propofol alone versus its use with adjunctive sedatives[5,6,8,12-19]. However, these studies included insufficient numbers of patients to produce significant and conclusive results regarding the differences between propofol and alternative sedation. In this study, we perform a systematic review and meta-analysis comparing sedation with propofol to traditional sedatives (with or without propofol) during endoscopic procedures.

MATERIALS AND METHODS

Protocol and registration

A protocol was established and documented prior to initiating the study to specify eligibility criteria and analytical methods for the studies included in this systematic review and meta-analysis in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was documented in a protocol registered in International Prospective Register of Systematic Reviews (PROSPERO) database (CRD 42017057305)[20].

Eligibility criteria

Eligibility criteria were based on population, intervention, comparison, outcomes and study design strategy. Only randomized clinical trials with full texts published were included.

Search strategy, study selection and data collection process

A literature search was performed using MEDLINE, Scopus, EMBASE, the Cochrane Library, Scopus, LILACS, BVS, Cochrane Central Register of Controlled Trials, and The Cumulative Index to Nursing and Allied Health Literature databases. The last search in the literature was performed on March, 2019 with no restriction regarding the idiom or the year of publication. The titles and abstracts of all potentially relevant studies were screened for eligibility. Duplicates were removed. If necessary, we accessed complementary and supplemental information in the research protocols of the studies available on the online registration platforms (for example, Clinical Trials or PROSPERO). The reference lists of studies of interest were then manually reviewed for additional articles by cross checking bibliographies. Two reviewers (Delgado AAA and Ribeiro IB) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria as described below. Any differences were resolved by mutual agreement and in consultation with the third reviewer (de Moura DTH). For the systematic review, we included studies that m*et all* the eligibility criteria, and for the meta-analysis, those that allowed the extraction of data from text, tables or graphs. Selection process is summarized in Figure 1.

Inclusion criteria

(1) Adults (over 18 years of age); (2) Undergoing endoscopic examination of the gastrointestinal tract (including esophagogastroduodenoscopy. and colonoscopy); and (3) Outpatient and elective procedures.

Exclusion criteria

Studies meeting any of the following criteria were excluded: (1) Types of participants: (a) Under the age of 18 years; and (b) Group of patients with specific comorbidities (obesity, pregnant and lactating women, cardiovascular diseases, pulmonary diseases,

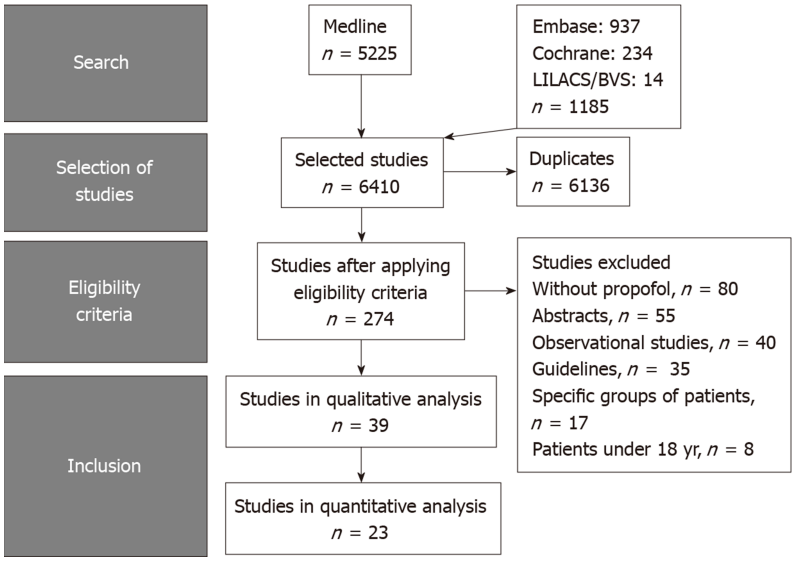


Figure 1 Flow diagram of included and excluded clinical trials.

ascites, renal failure and abdominal surgeries); (2) Types of intervention and outcomes: (a) Studies not using propofol in one of the treatment arms; (b) Studies that did not evaluate the outcomes of interest; and (c) Studies without extractable data; and (3) Intervention and control: (a) Patients receiving propofol alone or in combination with traditional combined sedative agents (benzodiazepines and opioids); and (b) Traditional combined sedatives (benzodiazepines and opioids) with or without concurrent propofol use.

Data items

The following data were collected for each trial: (1) Patient characteristics; (2) Characteristics of intervention and comparison: Type of medication, doses, form of application; and (3) Outcomes as previously described.

To simplify our analysis and data representation, we chose to subdivide the included studies into different groups according to the sedation regimens administered to the intervention and control groups (Table 1), as follows: (1) Group I - propofol *vs* benzodiazepine and opioid; (2) Group II - propofol *vs* propofol, benzodiazepine and/or opioid; and (3) Group III - propofol, benzodiazepine and opioid *vs* benzodiazepine and opioid.

Risk of bias in individual studies

As treatment effect size may differ due to detection, performance, selection, and bias, the methodological evaluation of the studies was performed. The adequacy of blinding, randomization, description of withdrawals and dropouts were determined by two authors working independently, using the Jadad scale[21] for the evaluation of randomized clinical trials.

Statistical analysis

This meta-analysis was performed using intention-to-treat data when possible. For all outcomes, absolute or mean risk difference was calculated. We considered statistically significant differences with 95%CI, $P < 0.05$, using the Mantel Hantzel tests (categorical variables) or inverse variance (continuous variables).

The effects of the treatment were expressed graphically through forest plots and the heterogeneity of the studies were evaluated by the method proposed by Higgins *et al*, denominated I^2, seeking values lower than 50%, using the fixed effect model. Risk of bias amongst studies was assessed using funnel plot analysis.

For treatment effects in which there is strong heterogeneity (I^2 - 50%) test with fixed effect, we exclude studies that were outside the limits of the funnel plot and the heterogeneity was reevaluated. If there was a reduction in heterogeneity ($I^2 < 50\%$), the excluded study was considered an outlier, that is, responsible for the high heterogeneity due to a publication bias and, consequently, it was not part of the final meta-analysis. If an outlier was not identified and the heterogeneity remained high, the Higgins *et al* test was randomly selected. Review Manager 5 (RevMan 5) version 5.39 (by the Cochrane Collaboration, 2015) was the software chosen to run the meta-analysis.

Table 1 Characteristics of the studies included in the meta-analysis

Author	Ref.	Country	Year	Patients (*n* = 3854)	Interven-tion	Interven-tion (*n* = 1834)	Control	Control (*n* = 2004)	Procedure	Jadad
Seifert	[19]	Germany	2000	239	PROP	120	PROP + MDZ	119	Endoscopy/ ERCP	5
Sipe	[38]	USA	2002	80	PROP	40	MDZ + MEP	40	Colono-scopy	4
Vargo	[34]	USA	2002	75	PROP	38	MDZ + MEP	37	ERCP/EUS	4
Ulmer	[39]	USA	2003	100	PROP	50	MDZ + FTN	50	Colono-scopy	4
Riphaus	[40]	Germany	2005	150	PROP	75	MDZ + MEP	75	ERCP	5
VanNatta	[12]	USA	2006	200	PROP	50	FTN + PROP/MDZ + PROP/MDZ + FTN + PROP	150	Colono-scopy	3
Fanti	[41]	Italy	2007	270	PROP	135	PROP + MDZ	135	EUS	5
Dewitt	[43]	USA	2008	80	PROP	40	MDZ + MEP	40	EUS	5
Kongkam	[42]	Thailand	2008	134	PROP	67	MDZ + MEP	67	ERCP	4
Schilling	[44]	Germany	2009	150	PROP	75	MDZ + MEP	75	ERCP/EUS/ Enteroscopy	5
Pascual	[25]	Cuba	2011	512	PROP	256	MDZ + MEP	256	Colono-scopy	4
Lee	[24]	Korea	2011	222	PROP + MDZ + MEP	102	MDZ + MEP	104	Endoscopy/ ERCP	5
Chun	[30]	Korea	2012	135	PROP	67	PROP + MDZ	68	Stomach ESD	3
Angsuwatcharakon	[29]	Thailand	2012	205	PROP + MDZ + MEP	103	MDZ + MEP	102	ERCP	3
Lee	[28]	Korea	2012	206	PROP	104	PROP + MDZ + FTN	102	ERCP/EUS	5
Zuo	[27]	China	2012	100	PROP	49	MDZ + FTN	51	Endomicroscopy	5
Levitzky	[26]	USA	2012	110	PROP + MDZ + FTN	55	MDZ + FTN	55	Endoscopy	3
Gurbulak	[32]	Turkey	2014	124	PROP	62	MDZ + MEP	62	Colono-scopy	5
Chan	[31]	Taiwan	2014	220	PROP	110	PROP + MDZ + AFTN	110	Endoscopy + colonoscopy	5
Hsu	[35]	Taiwan	2015	100	PROP	50	PROP + MDZ +FTN	50	Endoscopy + colonoscopy	1
Haytural	[33]	Turkey	2015	90	PROP	30	PROP + FTN/PROP + RFTN	60	ERCP	1
Li	[37]	China	2016	90	PROP	30	PROP + FTN	60	Colono-scopy	3
Schroeder	[36]	USA	2016	262	PROP	126	MDZ + FTN	136	Colono-scopy	4

MDZ: Midazolam; FTN: Fentanyl; PROP: Propofol; MEP: Meperidine; RFTN: Remifentanil; AFTN: Alfentanil.

Risk of bias across studies

Reporting bias across studies was evaluated by funnel plot graphical analysis. For each trial, the treatment effect was plotted against the measure of study precision and by Egger's test[22]. Asymmetrical funnel plot suggests the presence of reporting bias, methodological bias or true heterogeneity between smaller and larger studies.

Additional analysis

In the presence of an asymmetrical funnel plot or high heterogeneity, ($I^2 \geq 50\%$) a

sensitivity analysis was conducted to explore how the results of the meta-analysis could change under different assumptions[23]. Heterogeneity and funnel plot analysis before and after the removal of each study from the meta-analysis were assessed to identify the studies accounting for inconsistency among trials. If heterogeneity was reduced to below 50% after the removal of the outlier, the corrected intervention effect estimate was applied and the results were interpreted with caution. If inconsistency did not decrease, it was considered true heterogeneity.

RESULTS

Search and study selection

Among the 6410 articles screened from our initial search strategy, 23 randomized controlled studies were selected, including a total of 3854 patients[12,19,24-44]. Figure 1 summarizes the selection process of the studies.

Of the 3854 patients included, 1574 received propofol as the sole sedative while 2280 received midazolam, meperidine, fentanyl, remifentanil, alfentanil in combination with propofol (Table 1). There was wide geographical representation of studies included, encompassing a wide diversity of endoscopic procedures. The Jadad score was greater than 3 in 91.3% of the studies included in the meta-analysis, suggesting adequate methodological quality of these studies. All studies are available online, in full text format.

Results by groups

Group I: In 11 studies evaluating the incidence of bradycardia, there were no observed differences between both treatment arms (RD: -0.01, 95%CI: −0.03–+0.01, I^2: 22%, Figure 2A). In 10 studies assessing hypotension, no difference existed between both arms (RD: 0.01, 95%CI: −0.02–+0.04, I^2: 0%, Figure 2B). The incidence of desaturation was higher in the propofol group however this did not reach statistical significance (RD: −0.03, 95%CI: −0.06–+0.00, I^2: 25%, Figure 2C). Patient satisfaction with the visual analog scale was available in 6 of the included studies with a trend towards greater satisfaction in the benzodiazepine and/or opioid group (MD: +0.89, 95%CI: +0.62–+1.17, I^2: 39%, Figure 2D). Endoscopist satisfaction with sedation was evaluated in only 2 studies without differences observed between both arms (MD: −0.02, 95%CI: −0.20–+0.16, I^2: 0%, Figure 2E). Recovery time after the procedure was evaluated in 7 studies and revealed high heterogeneity. Even after withdrawal of the outlier, there was no statistical difference in recovery time between both arms (MD: -15.15, 95%CI: −31.85–+1.56, I^2: 99%, Figure 2F).

Group II: Bradycardia was assessed in 5 of the included studies and had a greater trend of occurrence in the Propofol arm with benzodiazepine and/or opioid-associated compared to the propofol alone arm (RD: -0.08, 95%CI: −0.13–−0.02, I^2: 59%, Figure 3A). In 6 studies assessing hypotension, there was no difference between the both arms (RD: -0.00, 95%CI: −0.08–+0.08, I^2: 85%, Figure 3B). Desaturation was evaluated in 7 studies without significant difference (RD: −0.00, 95%CI: −0.03–+0.02, I^2: 44%, Figure 3C). Patient satisfaction with the visual analog scale was available in 2 of the included studies and was different between both arms (MD: -0.62, 95%CI: -1.38–+0.13, I^2: 89%, Figure 3D). The recovery time after the procedure was evaluated in 7 studies and the result showed high heterogeneity without statistical difference between the groups (MD: -2.04, 95%CI: −6.96–+2.88, I^2: 97%, Figure 3E). The total dose of propofol was evaluated in 5 articles and was noted to be higher in the propofol with benzodiazepine and/or opiates arm but with high heterogeneity. The funnel-plot test did not demonstrate outliers (MD: 70.36, 95%CI: +53.11–+87.60, I^2: 61%, Figure 3F).

Group III: Two studies examined the incidence of bradycardia which was not different between sedation arms (RD: -0.00, 95%CI: −0.002–+0.02, I^2: 3%, Figure 4A). Additionally, two studies examining the incidence of hypotension showed no statistically significant differences between sedation arms (RD: 0.04, 95% CI: −0.05–+0.13, I^2: 77%, Figure 4B). Desaturation, however, evaluated in two studies was more commonly seen with propofol + benzodiazepine + opioid arm but with high heterogeneity (RD: 0.15, 95%CI: 0.08–+0.22, I^2: 95%, Figure 4C).

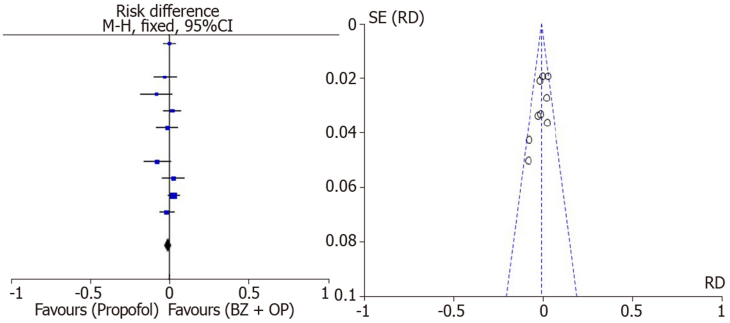
DISCUSSION

The use of propofol in endoscopy is increasingly common[45-47] for both diagnostic and advanced therapeutic procedures[47,48,57,49-56]. Propofol has proven to be safe and

A

Study or subgroup	Propofol Events	Propofol Total	BZ + OP Events	BZ + OP Total	Weight	Risk difference M-H, fixed, 95%CI
Zuo 2012	0	49	0	51	8.2%	0.00 [-0.04, 0.04]
Pascual 2011	0	0	0	0		Not estimable
Sipe 2002	0	40	1	40	6.6%	-0.03 [-0.09, 0.04]
Vargo 2002	0	38	3	37	6.2%	-0.08 [-0.18, 0.02]
Ulmer 2003	1	50	0	50	8.2%	0.02 [-0.03, 0.07]
Riphaus 2005	3	77	4	78	12.8%	-0.01 [-0.08, 0.05]
Dewitt 2008	0	0	0	0		Not estimable
Kongkam 2008	2	67	7	67	11.0%	-0.07 [-0.16, 0.01]
Schilling 2009	5	76	3	75	12.4%	0.03 [-0.05, 0.10]
Schoroeder 2016	6	144	2	45	23.8%	0.03 [-0.01, 0.07]
Gurbulak 2014	0	65	1	65	10.7%	-0.02 [-0.06, 0.03]
Total (95%CI)		606		608	100.0%	-0.01 [-0.03, 0.01]
Total events	17		21			

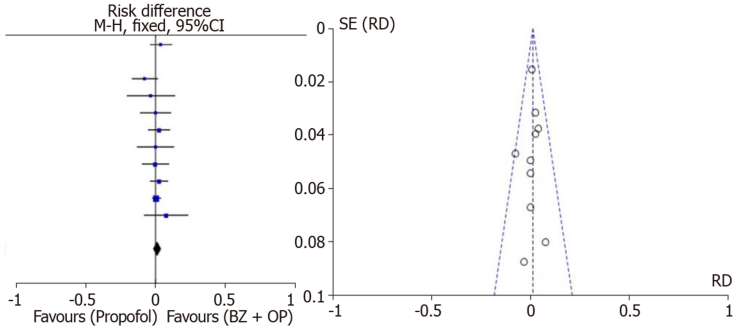
Heterogeneity: Chi^2 = 10.28, df = 8 (P = 0.25); I^2 = 22%
Test for overall effect: Z = 0.63 (P = 0.53)



B

Study or subgroup	Propofol Events	Propofol Total	BZ + OP Events	BZ + OP Total	Weight	Risk difference M-H, fixed, 95%CI
Zuo 2012	3	52	1	52	8.0%	0.04 [-0.04, 0.11]
Pascual 2011	0	0	0	0		Not estimable
Sipe 2002	0	40	3	40	6.2%	-0.07 [-0.17, 0.02]
Vargo 2002	6	38	7	37	5.8%	-0.03 [-0.20, 0.14]
Ulmer 2003	4	50	4	50	7.7%	0.00 [-0.11, 0.11]
Riphaus 2005	6	77	4	78	11.9%	0.03 [-0.05, 0.10]
Dewitt 2008	4	44	4	40	6.2%	0.00 [-0.13, 0.13]
Kongkam 2008	6	67	6	67	10.3%	0.00 [-0.10, 0.10]
Schilling 2009	4	76	2	75	11.6%	0.03 [-0.04, 0.09]
Schoroeder 2016	3	144	2	145	22.3%	0.01 [-0.02, 0.04]
Gurbulak 2014	22	65	17	65	10.0%	0.08 [-0.08, 0.23]
Total (95%CI)		649		649	100.0%	0.01 [-0.02, 0.04]
Total events	58		50			

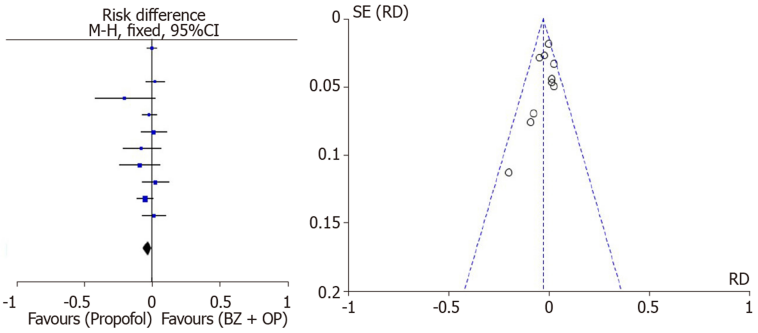
Heterogeneity: Chi^2 = 5.43, df = 9 (P = 0.80); I^2 = 0%
Test for overall effect: Z = 0.83 (P = 0.41)



C

Study or subgroup	Propofol Events	Total	BZ + OP Events	Total	Weight	Risk difference M-H, fixed, 95%CI
Zuo 2012	0	52	0	52	8.0%	0.00 [-0.04, 0.04]
Pascual 2011	0	0	0	0		Not estimable
Sipe 2002	1	40	0	40	6.2%	0.03 [-0.04, 0.09]
Vargo 2002	14	38	21	37	5.8%	-0.20 [-0.42, 0.02]
Ulmer 2003	0	50	1	50	7.7%	-0.02 [-0.07, 0.03]
Riphaus 2005	8	77	7	78	11.9%	0.01 [-0.08, 0.11]
Dewitt 2008	3	44	6	40	6.2%	-0.07 [-0.21, 0.06]
Kongkam 2008	15	67	21	67	10.3%	-0.09 [-0.24, 0.06]
Schilling 2009	9	76	7	75	11.6%	0.03 [-0.07, 0.12]
Schoroeder 2016	6	144	13	145	22.3%	-0.05 [-0.10, 0.01]
Gurbulak 2014	5	65	4	65	10.0%	0.02 [-0.07, 0.10]
Total (95%CI)		649		649	100.0%	-0.03 [-0.06, 0.00]
Total events	61		80			

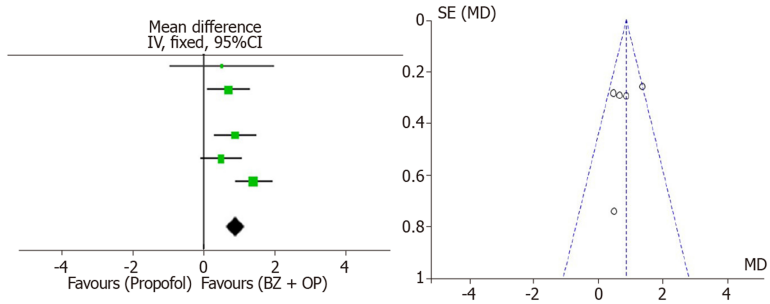
Heterogeneity: Chi^2 = 12.05, df = 9 (P = 0.21); I^2 = 25%
Test for overall effect: Z = 1.85 (P = 0.06)



D

Study or subgroup	Propofol Mean	SD	Total	BZ + OP Mean	SD	Total	Weight	Mean difference IV, fixed, 95%CI	Year
Vargo 2002	9.01	0.3	38	8.49	4.5	37	3.5%	0.52 [-0.93, 1.97]	2002
Sipe 2002	9.3	1.1	40	8.6	1.5	40	22.2%	0.70 [0.12, 1.28]	2002
Ulmer 2003	9.3	1.4	50	9.4	0.9	50	0.0%	-0.10 [-0.56, 0.36]	2003
Riphaus 2005	8.5	1.9	77	7.6	1.8	78	21.7%	0.90 [0.32, 1.48]	2005
Dewitt 2008	9.4	1	40	8.9	1.5	40	23.7%	0.50 [-0.06, 1.06]	2008
Schoroeder 2016	9.8	1.28	144	8.39	2.83	145	28.9%	1.41 [0.90, 1.92]	2016
Total (95%CI)			339			340	100.0%	0.89 [0.62, 1.17]	

Heterogeneity: Chi^2 = 6.60, df = 4 (P = 0.16); I^2 = 39%
Test for overall effect: Z = 6.45 (P < 0.00001)



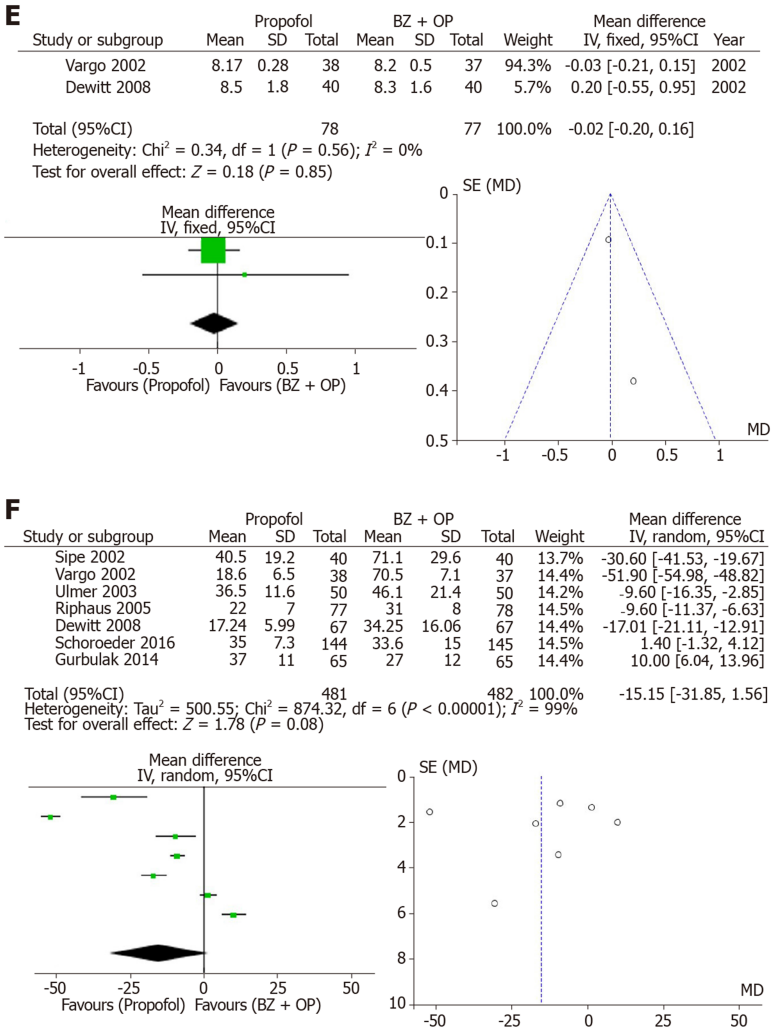


Figure 2 Propofol *vs* benzodiazepine associated with opioid - Forest plot of the meta-analysis. A: Comparing the occurrence of bradycardia between the propofol group and the benzodiazepine + opioid group (BZ + OP). Outcome: Bradycardia (defined as heart rate less than 50 bpm); B: Comparing the occurrence of oxygen desaturation between the propofol group and BZ + OP. Outcome: Hypotension (Defined as systolic blood pressure < 90 mmHg); C: Comparing the occurrence of desaturation between the propofol group and BZ + OP. Outcome: Oxygen desaturation (Defined as peripheral saturation of O_2 defined as < 90%); D: Comparing patient satisfaction with the sedation received for the procedure between the propofol group and BZ + OP. Outcome: Patient satisfaction (Visual analog scale – 0: very dissatisfied to 10: very satisfied); E: Comparing satisfaction of the endoscopists with the sedation administered for the procedure between the propofol group and BZ + OP. Outcome: Endoscopists satisfaction (Visual analog scale – 0: very dissatisfied to 10: very satisfied); F: Comparing patient recovery time after the procedure between the propofol group and BZ + OP. Outcome: Post procedure time to recovery (min).

affordable, yielding satisfactory and efficient sedation for patients undergoing endoscopy[58]. Propofol can be used as a single agent for anesthesia induction and maintenance, leads to rapid induction of anesthesia, carries a low half-life and is associated with fast recovery from anesthesia[45]. However, Propofol can be associated with dose-dependent complications, including the risk of major respiratory depression and several cardiovascular adverse events[53,59].

Our study adds to the plethora of literature describing the use of propofol for endoscopy sedation, but also highlights how it compares to numerous alternative and adjunctive sedatives.

After analyzing 23 clinical trials[12,19,24-44], many of good quality and adequate methodological design, including a total of 3854 patients, we note no significant differences in many outcomes measures between the sedation arms involving propofol alone or in combination with alternative sedatives.

In contrast to the last meta-analysis published[54], our study demonstrates no statistical difference in outcome measures with regards to hypotension, oxygen desaturation and post-procedure anesthetic recovery when using propofol alone or in combination with benzodiazepines and/or opioids.

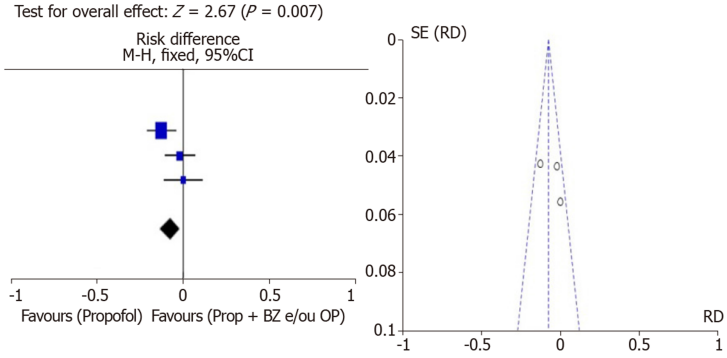
There was a trend towards increased incidence of bradycardia in patients in the

A

Study or subgroup	Propofol Events	Total	Propofol+BZ e/ou OP Events	Total	Weight	Risk difference M-H, fixed, 95%CI	Year
Seifert 2000	0	120	0	119	0.0%	0.00 [-0.02, 0.02]	2000
Lee 2012	0	107	0	106	0.0%	0.00 [-0.02, 0.02]	2012
Chan 2014	8	120	23	120	57.1%	-0.13 [-0.21, -0.04]	2014
Hsu 2015	2	50	3	50	23.8%	-0.02 [-0.11, 0.07]	2015
Li 2016	2	30	4	60	19.0%	0.00 [-0.11, 0.11]	2016
Total (95%CI)		200		230	100.0%	-0.08 [-0.13, -0.02]	
Total events	12		30				

Heterogeneity: Chi^2 = 4.85, df = 2 (P = 0.09); I^2 = 59%

Test for overall effect: Z = 2.67 (P = 0.007)

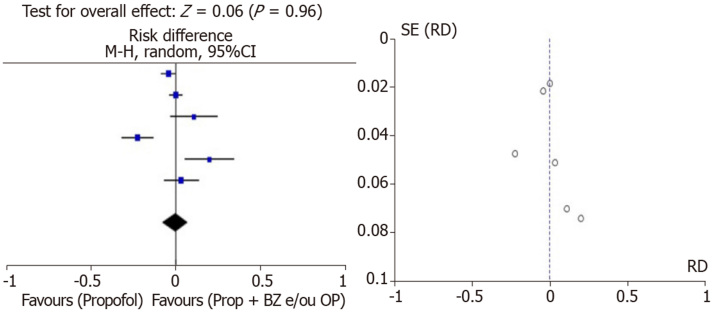


B

Study or subgroup	Propofol Events	Total	Propofol+BZ e/ou OP Events	Total	Weight	Risk difference M-H, random, 95%CI	Year
Seifert 2000	1	120	6	119	20.6%	-0.04 [-0.08, 0.00]	2000
Lee 2012	2	107	2	106	21.0%	-0.00 [-0.04, 0.04]	2012
Chun 2012	18	67	11	68	13.0%	0.11 [-0.03, 0.24]	2012
Chan 2014	8	120	35	120	16.8%	-0.23 [-0.32, -0.13]	2014
Hsu 2015	14	50	4	50	12.5%	0.20 [0.05, 0.35]	2015
Li 2016	2	30	2	60	16.1%	0.03 [-0.07, 0.13]	2016
Total (95%CI)		494		523	100.0%	-0.00 [-0.08, 0.08]	
Total events	45		60				

Heterogeneity: Tau^2 = 0.01; Chi^2 = 34.44, df = 5 (P < 0.00001); I^2 = 85%

Test for overall effect: Z = 0.06 (P = 0.96)

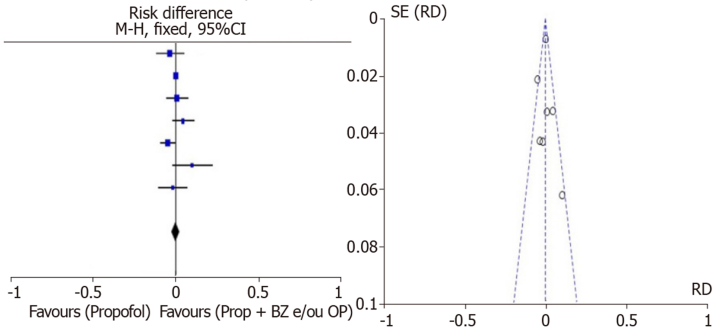


C

Study or subgroup	Propofol Events	Total	Propofol+BZ e/ou OP Events	Total	Weight	Risk difference M-H, fixed, 95%CI	Year
Seifert 2000	13	120	17	119	18.7%	-0.03 [-0.12, 0.05]	2000
Fanti 2007	0	135	0	135	21.1%	0.00 [-0.01, 0.01]	2007
Lee 2012	7	107	6	106	16.7%	0.01 [-0.06, 0.07]	2012
Chun 2012	4	67	1	68	10.6%	0.04 [-0.02, 0.11]	2012
Chan 2014	0	120	6	120	18.8%	-0.05 [-0.09, -0.01]	2014
Hsu 2015	8	50	3	50	7.8%	0.10 [-0.02, 0.22]	2015
Li 2016	1	30	3	60	6.3%	-0.02 [-0.10, 0.07]	2016
Total (95%CI)		629		658	100.0%	-0.00 [-0.03, 0.02]	
Total events	33		36				

Heterogeneity: Chi^2 = 10.77, df = 6 (P = 0.10); I^2 = 44%

Test for overall effect: Z = 0.23 (P = 0.82)



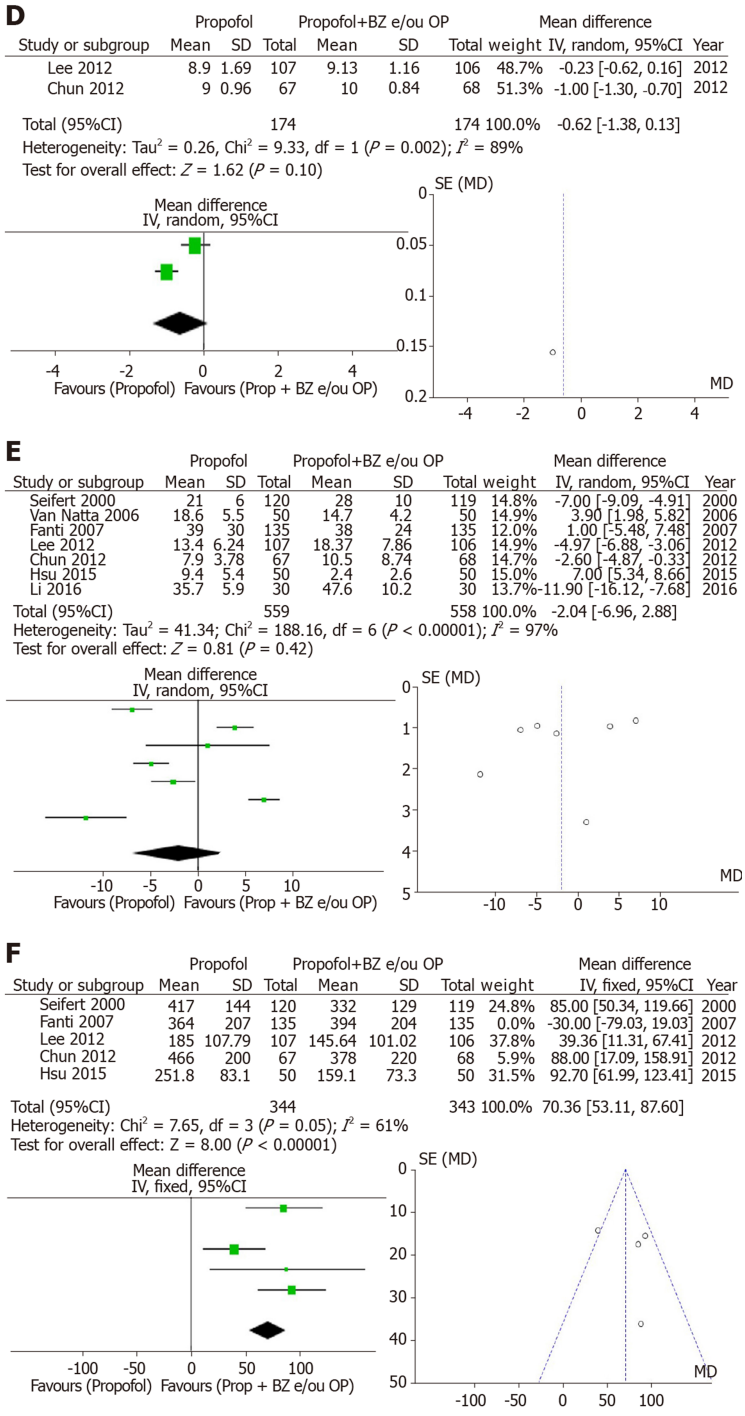


Figure 3 Propofol *vs* propofol with benzodiazepine and/or opioids - Forest plot of the meta-analysis. A: Comparing the occurrence of bradycardia between the propofol group and the propofol group associated with benzodiazepine and / or opioid (Prop + BZ and/or OP). Outcome: Bradycardia (defined as HR < 50 bpm); B: Comparing the occurrence of hypotension between the propofol group and (Prop + BZ and/or OP). Outcome: Hypotension (Defined as systolic blood pressure < 90 mmHg); C: Comparing the occurrence of desaturation between the propofol group and Prop + BZ and/or OP. Outcome: Desaturation (Defined as peripheral oxygen saturation of < 90%); D: Comparing patient satisfaction with sedation received for the procedure between propofol group and Prop + BZ and/or OP. Outcome: Patient satisfaction (Visual analog scale - 0 very dissatisfied / 10 very satisfied); E: Comparing patient recovery time after the procedure between the propofol group and Prop + BZ and/or OP. Time to recovery (min); F: Comparing the total dose of propofol administered during procedures between the propofol group and Prop + BZ and/or OP. Outcome: Total dose of propofol given during the procedure (mg).

propofol with benzodiazepine and opioid sedation arm compared to those on propofol alone. Incidence of bradycardia did not differ between other arms in the different treatment groups. No differences existed in recovery time between all sedation arms in all treatment groups as reported in the meta-analysis by Wang *et al*[60].

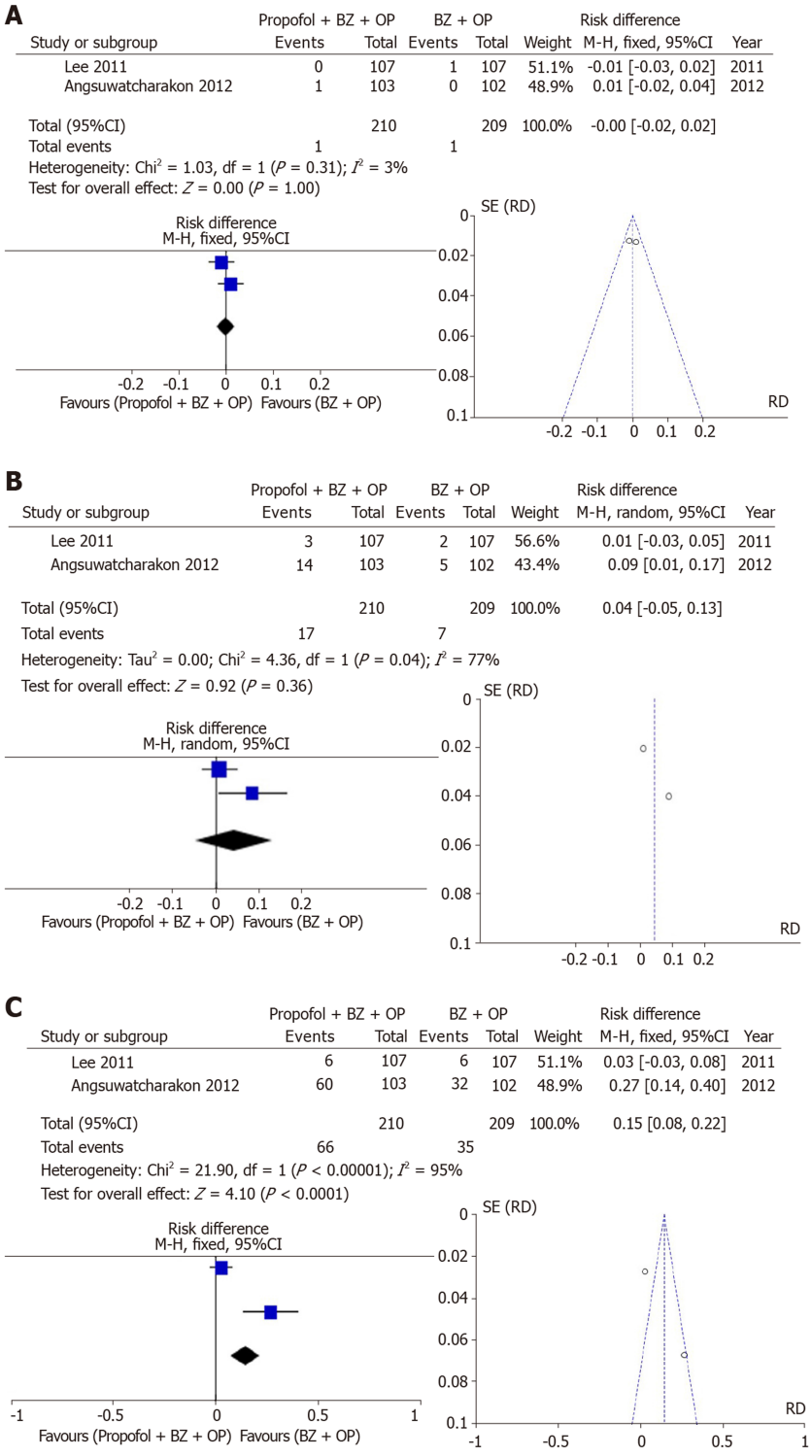


Figure 4 Propofol associated with benzodiazepine and opioid *vs* benzodiazepine associated with opioid - Forest plot of the meta-analysis. A: Comparing the occurrence of bradycardia between the benzodiazepine-associated propofol group and the opioid and the benzodiazepine group associated with the opioid (BZ + OP). Outcome: Bradycardia (defined as HR < 50 bpm); B: Comparing the occurrence of hypotension between the benzodiazepine-associated propofol group and the opioid and BZ + OP. Outcome: Hypotension (Systolic blood pressure < 90 mmHg); C: Comparing the occurrence of desaturation between the benzodiazepine-associated propofol group and the opioid and BZ + OP. Outcome: Desaturation (Peripheral saturation of O_2 < 90%).

Previous meta-analyses[2,3,60] also demonstrated significantly fewer adverse effects with propofol sedation. In our study, we observed that propofol used alone or in conjunction with other sedatives including opioids and benzodiazepines is safe and did not result in increased adverse events in patients undergoing endoscopic procedures as demonstrated by Sethi *et al*[54] which also included sedation for advanced endoscopic procedures such as endoscopic ultrasound, endoscopic

retrograde cholangiopancreatography, and double-balloon enteroscopy.

Due to the properties of propofol, its doses are very volatile[9,59]. Higher doses are associated with elevated cardiovascular risk and low doses are associated with several complications, especially in therapeutic procedures that cause pain. Propofol has a limited analgesic effect and higher doses are often required, when used as single agent for sedation in endoscopy. Several studies have reported that the combination of propofol with other sedative agents is a reasonable option to obtain the adequate depth of sedation, avoiding high dose-related side effects of propofol, allow for improve patient tolerance, prolong recovery time, and control of pain[5,13,15,17]. However, our study did not demonstrate an advantage to propofol alone without significant statistical differences when comparing propofol to alternative agents (with and without propofol).

In our meta-analysis, patient satisfaction with the use of a visual analog scale lead to a trend towards greater satisfaction for patients undergoing sedation with benzodiazepine and opioids when compared to propofol use. The satisfaction of the endoscopists was evaluated in a few studies included in this meta-analysis however did not reveal significant differences in endoscopists satisfaction.

There are several limitations to our analysis. Similar to prior publications and meta-analysis evaluating sedation in endoscopy, we observe high heterogeneity between the several studies aggregated in the meta-analysis, which must be taken into account in the interpretation of its results.

There are several reasons for heterogeneity present in the published literature for studies included. One reason may be due to intrinsic differences in populations examined with each study, specifically age, weight, body mass which may alter the amount of sedation required and tolerability. Additionally, the education level for various populations included may influence patient satisfaction levels. Another reason for heterogeneity is lack of uniformity between the comparisons made, the individual administering sedation (anesthesiologist, non-anesthetist physicians, certified registered nurse anesthetists), acceptable and max doses of sedatives, means of sedative administration (intermittent bolus *vs* continuous infusion) and criteria for re-administration of sedative if more is required. With regards to the procedures performed, diagnostic and therapeutic interventions can have differences in total procedure times, which in turn can influence the type of sedation, doses required, level of sedation and maintenance of sedation. This can certainly influence heterogeneity.

Finally, while it is important to highlight the clinical aspects of sedation use, it is imperative to understand that cost plays a significant role in the choice of sedation. While not assessed in this study, we believe cost effectiveness should be highlighted in future sedation meta-analysis.

In conclusion, this meta-analysis suggests that the use of propofol alone or in combination with traditional adjunctive sedatives is safe and does not result in an increase in negative outcomes.

ARTICLE HIGHLIGHTS

Research background

Endoscopy has transformed over the past several decades to encompass significant advances and procedural innovation, with the hope to provide better care for ill patients. However, with technical advances and innovation comes increasingly prolonged and complex procedures. This change in the endoscopic platform, alongside the higher acuity of patients, has demanded a change in the approach for procedural sedation to ensure safe interventions.

Research motivation

The change in the sedation landscape for endoscopy over the past several decades necessitates a better understanding of sedation types and how they compare to each other for the modern practicing endocsopist.

Research objectives

We aimed to compare sedation with propofol, alone or in combination with adjunctive sedations, to traditional sedation in endoscopy through a systematic review of the literature and meta-analysis.

Research methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered in International Prospective Register of Systematic Reviews international database. The search was performed in the electronic databases MEDLINE (*via* PubMed), LILACS (*via* BVS) and Cochrane/Central Register of Controlled Trials. The quality of the selected papers was evaluated by Jadad score and all articles used were selected by consensus of three authors.

Research results

A total of 23 clinical trials (n = 3854), from an initial search of 6410 articles, were included. For Group I (Propofol *vs* benzodiazepine and/or opioids): The incidence of bradycardia, hypotension, oxygen desaturation and post procedure recovery time was not statistically different between both arms. For Group II (Propofol *vs* propofol with benzodiazepine and/or opioids): Bradycardia tended to occur in the propofol group with benzodiazepine and/or opioid-associated but there was no statistical difference in the incidence of bradycardia, desaturation or recovery time between sedation arms. For Group III (Propofol with benzodiazepine and opioid *vs* benzodiazepine and opioid): Bradycardia, desaturation and, hypotension was not statistically significant between groups.

Research conclusions

Our findings suggest that the use of propofol alone or in combination with traditional adjunctive sedatives is safe and does not result in an increase in negative outcomes in patients undergoing endoscopic procedures.

Research perspectives

Future studies should consider methods for standardization of sedation use to allow for less heterogeneity amongst studies and to improve analysis in future metanalyses to come. Future studies should also highlight cost effectiveness of various sedations used.

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