

Safety and efficacy of propofol alone or in combination with other agents for sedation of patients undergoing colonoscopy: an updated meta-analysis

K. ZHANG¹, H. XU², H.-T. LI¹

¹Department of Painless Endoscopy, People's Hospital of Linzi District, Zibo City, Shandong Province, China, Affiliated Hospital of Binzhou Medical University, Shandong Province, China

²Department of Anesthesiology, People's Hospital of Linzi District, Zibo City, Shandong Province, China, Affiliated Hospital of Binzhou Medical University, Shandong Province, China

Abstract. – The aim of this meta-analysis was to assess the efficacy and safety of propofol sedation for colonoscopy in comparison with traditional sedative agents. We performed a systematic search of PubMed, Embase, Scopus, Web of Science CENTRAL (Cochrane Central Register of Controlled Trials) and Google Scholar databases to identify eligible randomized controlled trials (RCTs) published before November 2019, and compared the effect of traditional sedative agents (TA) with the effect of propofol/propofol combined with TAs for routine colonoscopy. We included 22 eligible trials in our analysis, with a total of 2575 participants. We found strong associations between propofol use and short recovery (SMD MD, -1.15 [-1.55, -0.75], $p < 0.00001$), procedure duration (SMD -0.28 [-0.55, -0.02], $p < 0.05$), discharge times (SMD = -0.71 [-1.06, -0.36], $p < 0.0001$), and sedation scores (SMD 1.29 [0.36, 2.22], $p < 0.05$). Propofol in combination with traditional agents led to a significant decrease in discharge time compared with the discharge times of traditional sedatives alone (SMD = -0.69 [-1.07, -0.31], $p < 0.0004$). The effects of propofol on cecal intubation rates, and occurrences of hypotension and apnea were similar to those of TAs. Our results suggest that propofol can be used as a safe alternative to TAs, and can significantly shorten procedure duration, recovery and discharge times, and improve sedation depth.

Key Words:

Propofol, Sedation, Colonoscopy, Meta-analysis.

Introduction

The majority of low-risk endoscopic procedures such as colonoscopy and esophagogastroduodenoscopy are performed with some form of

sedation¹. While the sedation rates vary throughout the world, over 98% of routine colonoscopies in the US use sedation². The use of sedation during colonoscopies decisively influences the quality of the procedure, and results in high polyp detection rates³. The standard colonoscopy protocol in the United States and Europe involves conscious sedation, using a combination of a benzodiazepines and opioid agents, such as midazolam, diazepam, remifentanyl and/or meperidine, pethidine, and fentanyl⁴. However, these agents carry risks of adverse effects (1:200 to 1:2000) and mortality, as a result of cardiorespiratory complications⁵.

Propofol (2,6-diisopropyl phenol) is often used for general anesthesia in combination with nitrous oxide and muscle relaxants, and induces conscious sedation at lower doses. Studies have suggested that propofol has significant benefits over other agents used for conscious sedation. It has no active metabolites and is efficiently and quickly cleared by the liver⁶. Since propofol has a significantly shorter half-life than other agents used for conscious sedation, patients experience much faster recovery from sedation⁷. However, reports of respiratory depression associated with propofol conscious sedation exist, and its effects cannot be reversed by a specific antagonist⁸. Randomized controlled studies (RCTs) have assessed the efficacy of propofol for colonoscopy with varying results. Zhang et al⁹ summarized the potential benefits of propofol sedation during colonoscopy, and concluded that it leads to shorter recovery, discharge, and ambulation times, and a more efficient sedation. However, the consistency of the results may

have been compromised by the significant heterogeneity among the included RCTs, resulting in potential bias.

We aimed to analyze and summarize current findings on the safety and efficacy of propofol as a sedative agent for colonoscopy incorporating more recent RCTs and including sub group analyses to evaluate the effects of propofol alone or in combination with other agents for sedation in patients undergoing colonoscopy.

Materials and Methods

Search Strategy

We performed this systematic review and meta-analysis following to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines. This study did not involve human or animal experiments, therefore, Ethical approval was not necessary. We identified relevant articles by searching PubMed, Embase, Scopus, Google Scholar, and Web of Science CENTRAL (Cochrane Central Register of Controlled Trials) databases for papers published before the 30th of November 2019 using the following search terms: (“propofol” OR “Propofol-fentanyl” AND “sedation” or “Traditional Sedative Agent” AND (“colonoscopy” OR “gastrointestinal surgery”). We also searched the references of the selected studies for additional possibly relevant publications.

Eligibility Criteria

We only included RCTs, case-control or cohort studies with adult patients who underwent colonoscopy with sedation done either using propofol alone or propofol in combination with another sedative agents, and compared with sedation using traditional sedative agents (TAs). Our measured outcomes included recovery time, procedure duration, time-to-discharge, sedation scores, and hypotension, apnea occurrence, and cecal intubation rates.

Risk of Bias in Individual Studies

We applied the Jadad score to evaluate the risk of bias in the selected studies.

Data Collection and Analysis

Two authors (K. Zhang and H. Xu) independently extracted the essential information from each included study. Their initial selection was at the level of the title and abstract, and

then they focused on the full-texts. We included variables about participants details, sedation methods, procedures, recovery times, procedure durations, discharge times, sedation scores, and complications rates (apnea and hypotension). Any disagreement was resolved by discussion.

Statistical Analysis

We used the Review Manager Statistical Software (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) to calculate standardized mean differences (SMDs), Odds ratios (ORs) with 95% Confidence Intervals (CIs), and publication bias. We also evaluated the heterogeneity among the included studies using the Cochran’s Q statistic and I² metric tests. If the I² was less than 50%, we used a fixed-effects model, otherwise we used a random-effects model to combine the results. We conducted sub-group analyses for the use of propofol in combination with traditional sedative agents. We applied the Begg and Egger’s test to assess publication bias. We considered *p*-values < 0.05 as statistically significant.

Results

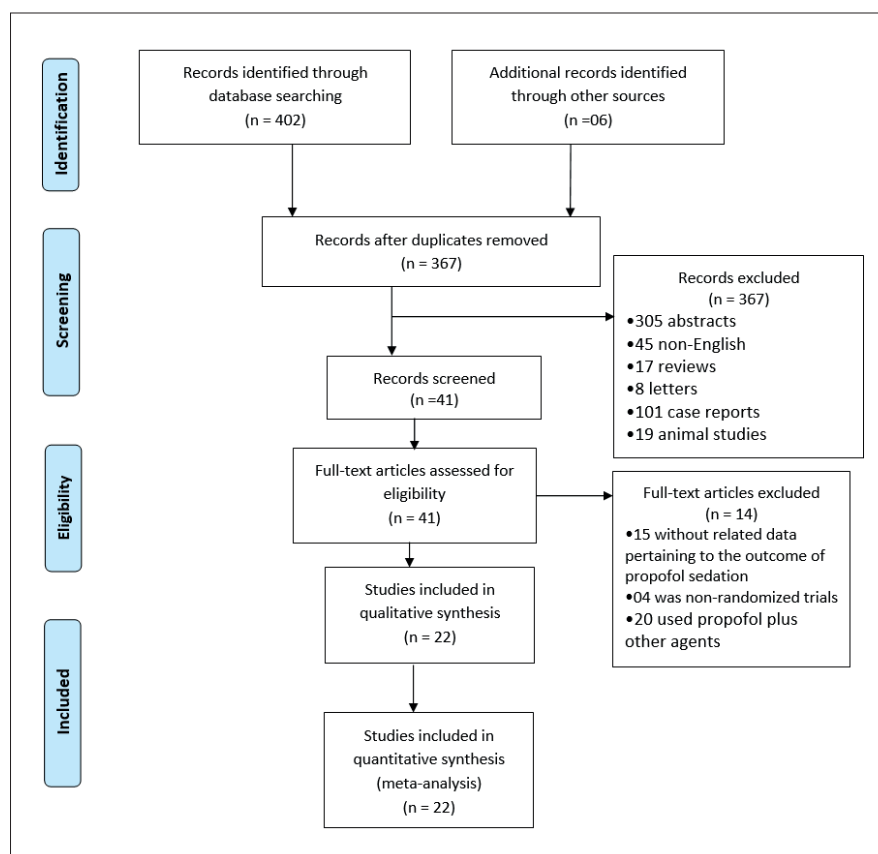
Literature Search

We retrieved 408 published articles from the systematic search during the initial screening. Out of those, we deleted 367 items (305 abstracts, 45 non-English, and 17 review papers) that were duplicate records. After the title and abstract review, we selected 41 potential studies for full-text review. Out of these papers, we excluded 15 due to lack of relevant data, and 4 that were not RCT studies. The remaining 22 studies met all the inclusion criteria and we included them in our meta-analysis (Figure 1).

Characteristics of Eligible Studies

Table I summarizes the characteristics of the selected prospective RCTs, published between 1994 and 2019, with a total of 2575 participants. The population sizes in each study varied between 14 and 300 participants. The dosage of propofol ranged from 0.3 mg/kg to 1 mg/kg. Out of 32 RCTs in the analysis, 18 evaluated recovery times, 14 evaluated procedure times, and 8 evaluated discharge times. The traditional sedative agents used in the RCTs included midazolam alone (4 studies), midazolam in combination with

Figure 1. Flow diagram of the selection of studies and specific reasons for exclusion from the meta-analysis.



fentanyl (5 studies), midazolam in combination with pethidine (2 studies), remifentanyl (4 studies), midazolam in combination with meperidine (3 studies), midazolam plus flumazenil (1 study), midazolam plus nalbuphine (1 study), fentanyl (1 study), fentanyl plus ketamine (1 study) diazepam in combination with pethidine/ meperidine (2 studies), midazolam/diazepam (1 study), and etomidate (1 study).

Recovery Time

Recovery time data were reported on 16 studies¹⁰⁻²⁵, with averages of 17.18 min in the propofol alone group (P), 27.3 min in the traditional agent (TA) group, and 15.5 min in the propofol combined with traditional agents (PTA) group. The mean recovery time for all the patients receiving propofol was 16.1 min. Our results suggested that patients in the P plus PTA groups had similar recovery times to those in the TA group (SMD, 95% CI, -0.59 [-1.21, 0.04]) (Figure 2) with significant heterogeneity ($I^2 = 98\%$, $p < 0.001$). Subgroup analysis demonstrated that propofol alone led to a significantly shorter recovery time than traditional sedative agents (10.12 min of sta-

tistically significant decrease; SMD -1.15 [-1.55, -0.75], $p < 0.00001$). While the recovery times were still 11.8 min shorter in the PTA group, but this difference was not significant (SMD -0.33 [-1.15, -0.50], $p = 0.44$).

A. Procedure Time

Procedure times were analyzed in 13 out of the 22 studies included in the analysis^{10,13,14,16,17,19-22,24-27}, with average procedure times at 18.4, 19.7 and 20.54 minutes in P, TA and PTA groups, respectively (Figure 3). Pooled results under our random effect model showed that the procedure times for patients in the P group was similar to that of the TA group (SMD = -0.01 [-0.20, 0.18]) (Figure 3), with significant heterogeneity ($I^2 = 67\%$, $p = 0.002$). The subgroup analysis showed that combining propofol with other agents resulted in procedure times similar to those observed with traditional sedative agents (SMD = 0.16 [-0.08, 0.40], $p = 0.9$). At the same time, use of propofol alone resulted in a significant drop in procedure times compared to those in the TA group (SMD = -0.28 [-0.55, -0.02], $p = 0.03$)

Table 1. Summary of randomized controlled trials included in the meta-analysis.

N.	Author, Year, country	Administrator	Sedation	No. of Patients	Male/Female	Age (Mean ± SD)	Recovery Time	Time-to-Discharge	Procedure Time	Jadad score
1	Ulmer et al, 2003, Usa	Endoscopists & Nurses	Propofol Midazolam + fentanyl	50	29/21	55.6 ± 11.2	16.5 ± 8.8	36.5 ± 11.9	-	5
2	Sipe et al, 2002, Usa	Nurses & physicians	Propofol Midazolam + meperidine	50	25/25	55.3 ± 11.8	27.5 ± 16.2	46.1 ± 21.4	-	4
3	Ng et al, 2001, Singapore	Patient controlled Anesthetist	Propofol Midazolam	40	19/21	51.7 ± 11.3	14.4 ± 6.5	40.5 ± 19.2	18.7 ± 5.5	4
4	Alatise et al, 2015, Nigeria	Gastroenterologist	Propofol + fentanyl + Midazolam	44	27/17	54 ± 15	33 ± 23.3	71.1 ± 29.6	23 ± 7.8	3
5	Bright et al, 2003, UK	Physicians & Nurses	40 mg propofol + 1 mg alfentanil 50 mg pethidine + 2.5 mg midazolam	44	21/23	49 ± 13	43.3 ± 12.1	42.3 ± 12.1	8.7 ± 3.9	3
6	Alkabay et al, 2006, Turkey	Physicians & Nurses	0.5 mg/kg propofol 0.5 µg/kg remifentanyl	40	23/17	56.6 ± 12.6	61 ± 29.7	-	8.7 ± 3.3	4
7	Padmanabhan et al, 2017, USA	Endoscopists & Nurses	Propofol Fentanyl + midazolam	40	26/14	57.8 ± 11.9	-	-	22.6 ± 7.4	4
8	Moerman et al, 2003, Belgium	Nurses & physicians	1 mg/kg propofol 0.5 µg/kg remifentanyl	34	19/15	41.7 ± 7.7	3 ± 1.7	40 ± 34.5	28.2 ± 7.7	3
9	Mandel et al, 2006, USA	Patient controlled Anesthetist	10 mg/ml propofol + 10 µg/ml remifentanyl 12.5 µg/ml fentanyl + 0.5 mg/ml midazolam	33	12/21	54 ± 15.5	0 ± 0	75 ± 34.5	15 ± 7.8	3
10	Ferreira et al, 2016, Portugal	Anesthetist & Nurses	Propofol Remifentanyl	50	28/22	40 (17-74)	2.1 ± 1.3	37.9 ± 9.1	22.9 ± 5.4	4
11	Schroeder et al, 2016, USA	Physicians & Nurses	60 mg propofol 2 mg midazolam + 50 µg fentanyl	49	26/23	48 (18-75)	1.2 ± 0.8	41.7 ± 11.7	18.8 ± 4.6	5
12	Liu et al, 2009, China	Physicians & Nurses	4.8 mg propofol + 125 µg alfentanil 0.035 mg/kg midazolam + 0.35 mg/kg meperidine	300	162/138	61.4 ± 9.8	-	38 ± 6	12.7 ± 3.5	3
13	Roseveare et al, 1998, UK	Endoscopists & Nurses	10 mg/ml propofol + 25 µg/ml alfentanil 50 mg pethidine + 10/20 mg diazepam	300	153/147	61.0 ± 9.4	3.1 ± 1.7	38.5 ± 7.8	13.3 ± 3.8	3
14	Reimann et al, 2000, Germany	Nurses & physicians	2 mg midazolam + 20-50 mg propofol 2 mg midazolam + 10-20 mg nalbuphine	20	5/15	41 ± 15	0 ± 0	-	-	3
				25	3/17	40 ± 11	4.9 ± 4.3	-	19 ± 9.9	3
				24	11/13	57.7 ± 10.8	32 ± 25	-	21 ± 12.3	3
				150	61/89	58.6 ± 13.8	58 ± 33	-	-	3
				127	50/77	55.4 ± 15.4	67 ± 29	-	-	3
				126	65/61	57.7 ± 13.4	35 ± 7.3	-	23 ± 9.1	3
				136	76/60	58.1 ± 13.8	33.6 ± 15.0	-	24.4 ± 9.3	3
				50	38/22	55 (43-63)	16.2 ± 4.2	-	23.7 ± 14.4	4
				50	27/23	48 (35-64)	1.9 ± 2.2	-	24.2 ± 15.6	4
				33	NR	52 (23-74)	10 ± 29.3	-	15 ± 5.9	2
				33	NR	50 (29-73)	40 ± 29.3	-	14 ± 8.3	2
				47	27/20	44 ± 12	5 ± 22.8	17 ± 96.6	-	3
				32	17/15	41 ± 12	23 ± 22.8	93 ± 96.6	-	3

Table continued

Table 1 (Continued). Summary of randomized controlled trials included in the meta-analysis.

N.	Author, Year, country	Administrator	Sedation	No. of Patients	Male/ Female	Age (Mean ± SD)	Recovery Time	Time-to-Discharge	Procedure Time	Jadad score
15	Lee et al, 2002, China	Gastroenterologist	4.8 mg propofol + 12 µg alfentanil 0.1 mg/kg diazepam + 0.5 mg/kg mepidine	50 50	26/24 28/22	72.4 ± 5.3 73.5 ± 6.1	1.2 ± 1.4 6.2 ± 1.4	- -	17.9 ± 9.9 16.8 ± 12.2	3
16	Paspatis G et al, 2002, Greece	Physicians & Nurses	2/3 mg midazolam+80 mg propofol 5 mg midazolam + 75 mg pethidine	64 56	33/31 29/27	61.4 ± 11 60.2 ± 11.5	- -	- -	- -	2
17	Kostash et al, 1994, USA	Physicians & Nurses	Propofol Midazolam/Diazepam	19 38	10/09 20/18	45.8 ± 18.4 40.9 ± 15.1	13.3 ± 15.7 24.7 ± 27.3	- -	23.4 ± 9.4 22.4 ± 10.5	2
18	Munoz-Navas et al 1994, USA	Physicians & Nurses	Propofol Midazolam + Flumazenil	14 15	NR NR	NR NR	18.0 ± 12.6 35.0 ± 12.6	20 ± 15.3 41 ± 15.3	- -	2
19	Adigun et al 2019, Nigeria	Physicians & Nurses	Propofol 0.5 mg/kg with Fentanyl 0.5 µg/kg midazolam 2.5 mg with pentazocine 15 mg	31 31	18/13 16/15	60.76 ± 11.32 61.62 ± 12.9	24 min 46 min	- -	- -	4
20	Kayaalti et al 2019, Turkey	Anesthetist & Nurses	1 mg midazolam and 30-50 mg propofol 50 mg ketamine + 50 mg fentanyl	30 30	16/14 17/13	53.2 ± 14.9 59.9 ± 11.8	- -	- -	- -	3
21	Kulling et al 2003, Switzerland	Physicians & Nurses	4.8 mg propofol + 125 µg alfentanil 0.35 mg/kg midazolam + 0.35 mg/kg meperidine	50 50	28/22 27/23	55 (43-63) 48 (35-64)	- -	- -	- -	3
22	Lee et al 2019, Korea	Nurses	Propofol Etomidate	62 62	37/25 41/21	71.26 ± 4.53 71.37 ± 5.20	- -	- -	29.46 ± 16.04 29.73 ± 12.23	4

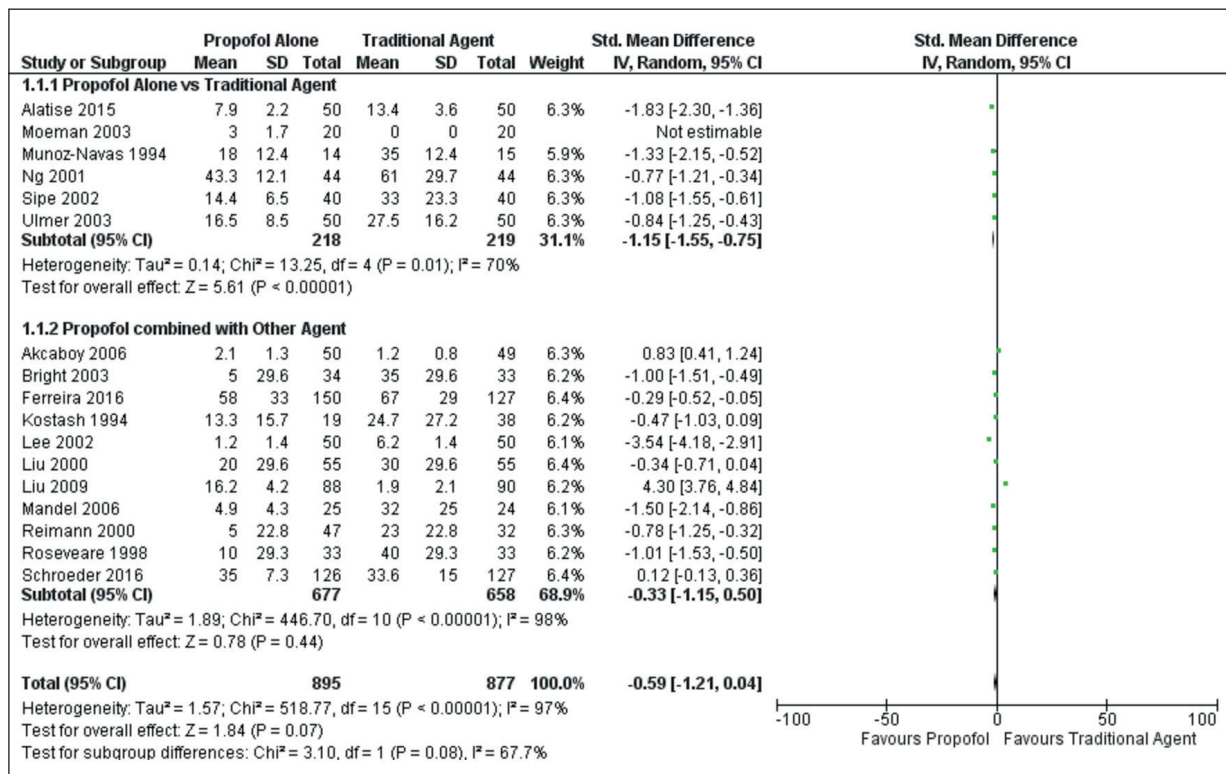


Figure 2. Forest plot comparing recovery times after propofol and after traditional agents.

B. Discharge Time

Discharge time was reported in 8 of the 22 studies^{12-17,23,26}. On average, patients that received propofol were discharged after 29.65 min. Patients in the P group (propofol alone) were discharged after 35.66 min, patients in the TA group were discharged after 58.42 min, and patients administered propofol in combination with TA were released after 31.63 min (Figure 4). The pooled estimate under the random effect model showed a significantly lower time-to-discharge for patients in the P groups (P and PTA together) compared to those in the TA group (SMD = -0.71 [-1.06, -0.36]). We found a significant heterogeneity between the studies analyzed (I² = 99%, p < 0.001). Our sub-group analysis further showed that propofol alone resulted in a not statistically significant reduction in discharge times (SMD = -0.73 [-1.24, -0.22], p = 0.05), while propofol in combination with TA led to a significant decrease in time-to-discharge compared to those after traditional sedatives (SMD = -0.69 [-1.07, -0.31], p < 0.0004) (Figure 4).

C. Sedation Score

Eight studies^{13-15,17,24,27-29} calculated sedation scores. Patients administered propofol showed significant changes in sedation scores compared to those in the TA group (OR = 0.85 [0.10, 1.60], p = 0.03). We found significant heterogeneity between the studies analyzed (I² = 99%, p < 0.001) (Figure 5). Our subgroup analysis showed small differences in sedation scores when propofol was used in combination with other agents (average score of 3.12 vs. 2.88 in TA group, OR = 0.29 [-0.86, 1.45], p = 0.62). However, in the subgroup of studies reporting the effect of propofol alone, the difference in sedation scores was statistically significant when compared to that in the TA group (average score of 3.98 in the P group vs. 2.88 in the TA group, OR = 1.29 [0.36, 2.22], p = 0.006).

D. Cecal Intubation

Eight studies^{13-15,17,21,23,24,30} reported data on cecal intubations (CI). The included studies reported 5 CI events when propofol was used as a sedative, and 2 events in the TA group (rates, 1.14 and 0.5% respectively). The

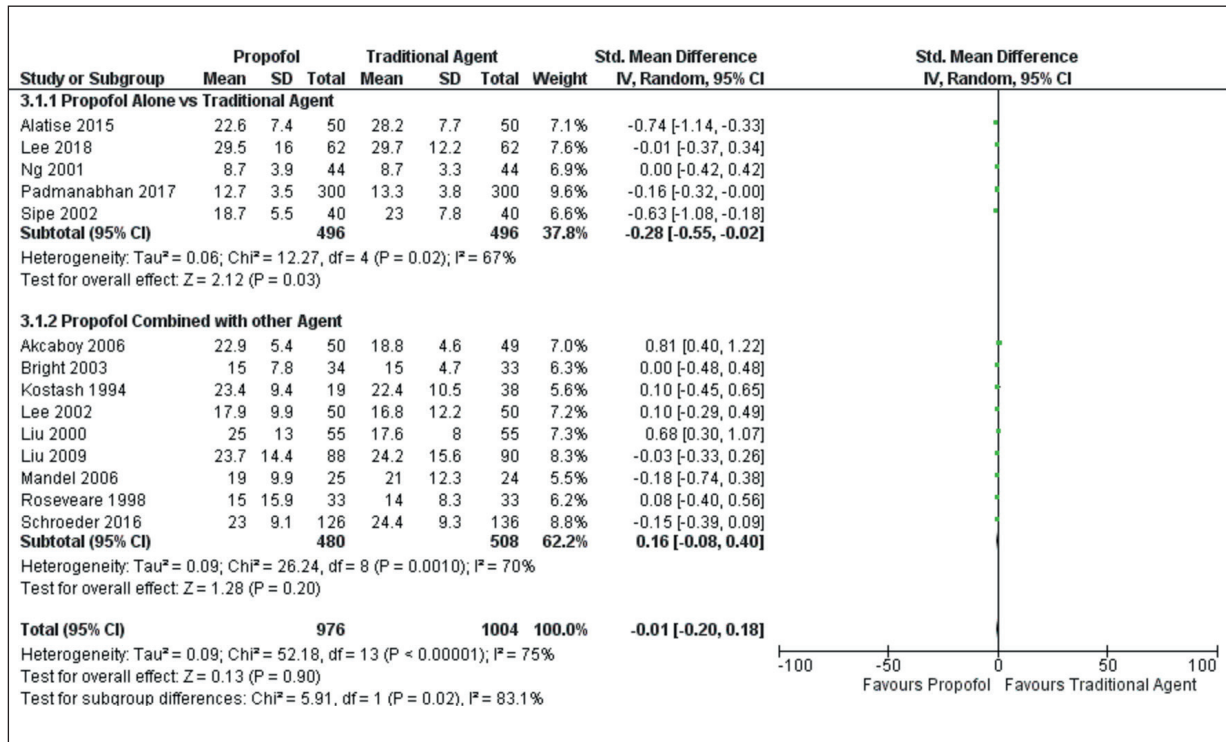


Figure 3. Forest plot comparing procedure lengths with propofol and those with traditional agents.

pooled estimate under our fixed effect model suggested that the propofol group had slightly higher CI rates than the TA group (Odds Ratio (M-H, Fixed, 95% CI, 1.41 [0.34, 5.82]), with insignificant heterogeneity (I² = 0%, p < 0.84; Figure 6).

E. Side Effects

We also analyzed the effect of propofol sedation on the possible adverse effects of conscious sedation such as hypotension and apnea. Twelve studies^{10,14,15,17,18,21,22,26-28,31} reported data on hypotension, and 8 reported data on ap-

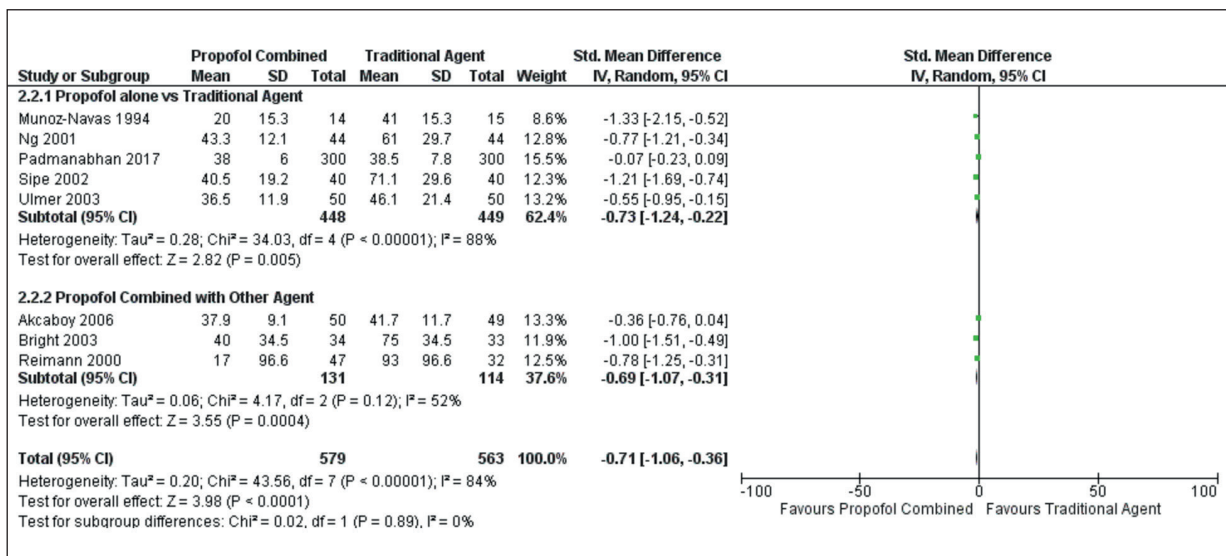


Figure 4. Forest plot comparing time-to-discharge after propofol and after traditional agents.

Propofol vs Tas for colonoscopy: a meta-analysis

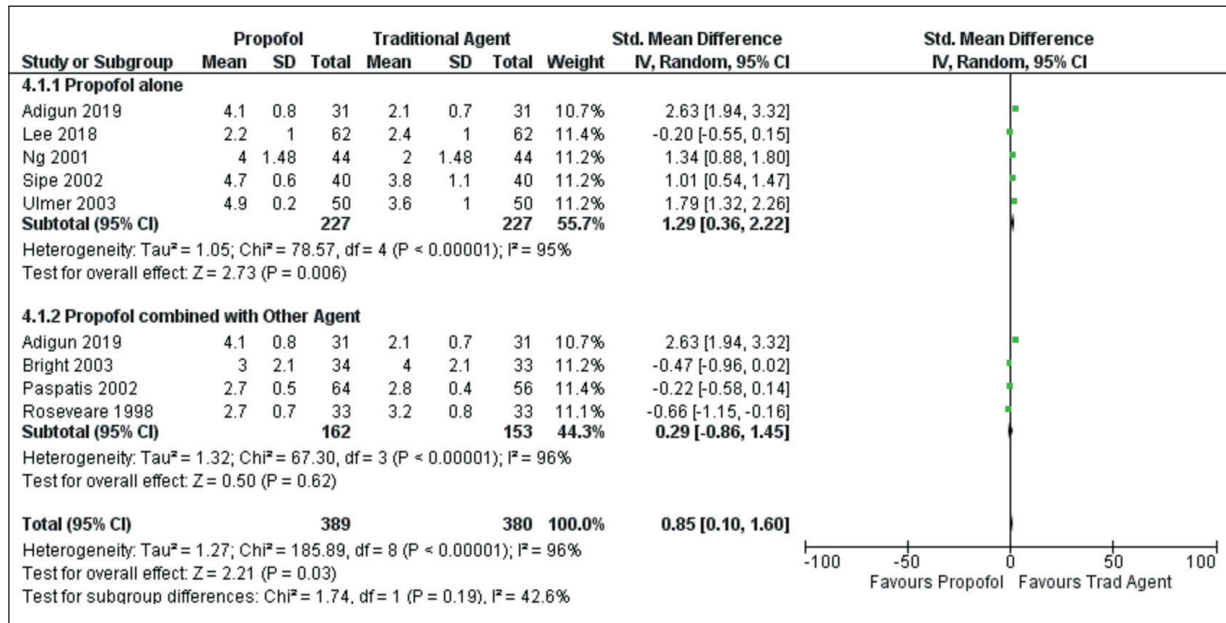


Figure 5. Forest plot comparing sedation scores with propofol and with traditional agents.

near^{11,13,14,23,24,26,30} occurrences. The pooled estimate under our fixed effect model suggested that propofol administration led to a slight insignificant increase in hypotension rates as compared to traditional sedation agents (rates, 9.78% in the P group vs. 7.76% in the TA group,

OR = 1.30 [0.93, 1.82]), with non-significant heterogeneity (I² = 35%, p < 0.11). We found a small insignificant increase in the hypotension rate in the PTA group, compared to that in the P group (9.78% and OR = 1.16 [0.72, 1.88] in the P group vs. 8.76% and OR = 1.45 [0.91, 2.31]

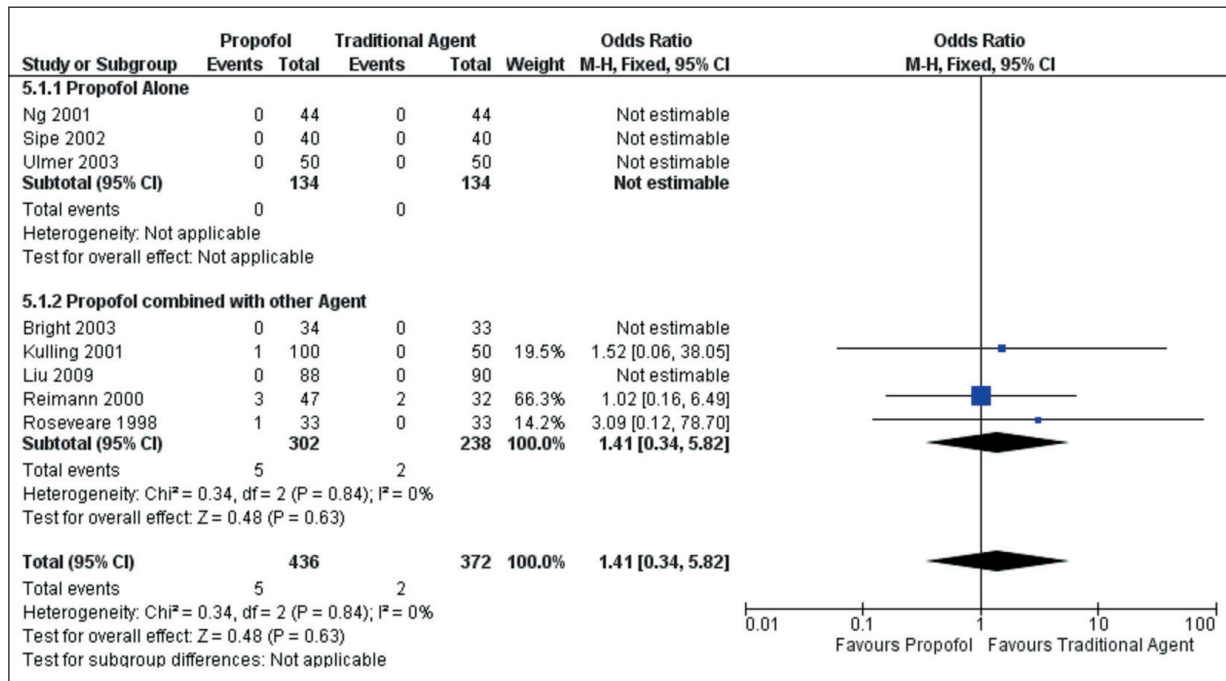


Figure 6. Forest plot comparing cecal intubation rates after propofol and after traditional agents.

in the PTA group). These results suggest that the effect of propofol on hypotension rates was not markedly affected by its combination with other sedatives (when comparing the P group vs. the PTA group; Figure 7).

Patients in the propofol group also showed a slight but non-significant reduction in apnea rates compared with the TA group (rates, 0.74% in the P group vs. 1.23% in the TA group; OR = 0.58 [0.13, 2.55]), with insignificant heterogeneity ($I^2 = 0\%$, $p = 0.48$; Figure 8).

Publication Bias

We used Begg’s funnel plots to assess the potential selection and performance publication biases. As shown in supplementary figures, the shape of the funnel plot suggests the absence of publication bias (Supplementary Figures 1, 2, 3, 4, 5, 6, 7).

Discussion

Our meta-analysis of 22 RCTs shows that propofol as a sedative during colonoscopy leads to shorter recovery and procedure times, and

higher sedation scores. Combination of propofol with other sedative agents significantly lowered the time-to-discharge compared to traditional sedative agents. The efficiency of the procedure, as indicated by the rate of cecum intubation rates in the propofol group was comparable with those in the patients administered traditional sedatives. Moreover, propofol was not associated with increased occurrences of adverse effects such as hypotension or apnea.

Our meta-analysis has demonstrated that propofol-mediated sedation is associated with overall faster recovery compared with sedation using benzodiazepines and opioids. The recovery time was 11.8 min shorter in patients receiving propofol alone, and 10.2 min shorter when propofol was used in combination with other sedative agents¹⁰⁻²⁵. The majority of RCTs that reported recovery rates, showed a consistently lower mean recovery time with propofol alone, with a pooled SMD at -1.15 [-1.55, -0.75], $p < 0.00001$ ^{10,12-15}. We discovered a significant heterogeneity in the included RCTs that can be explained by the differences in dosages and administration of sedatives, and by recovery time characteristics between the

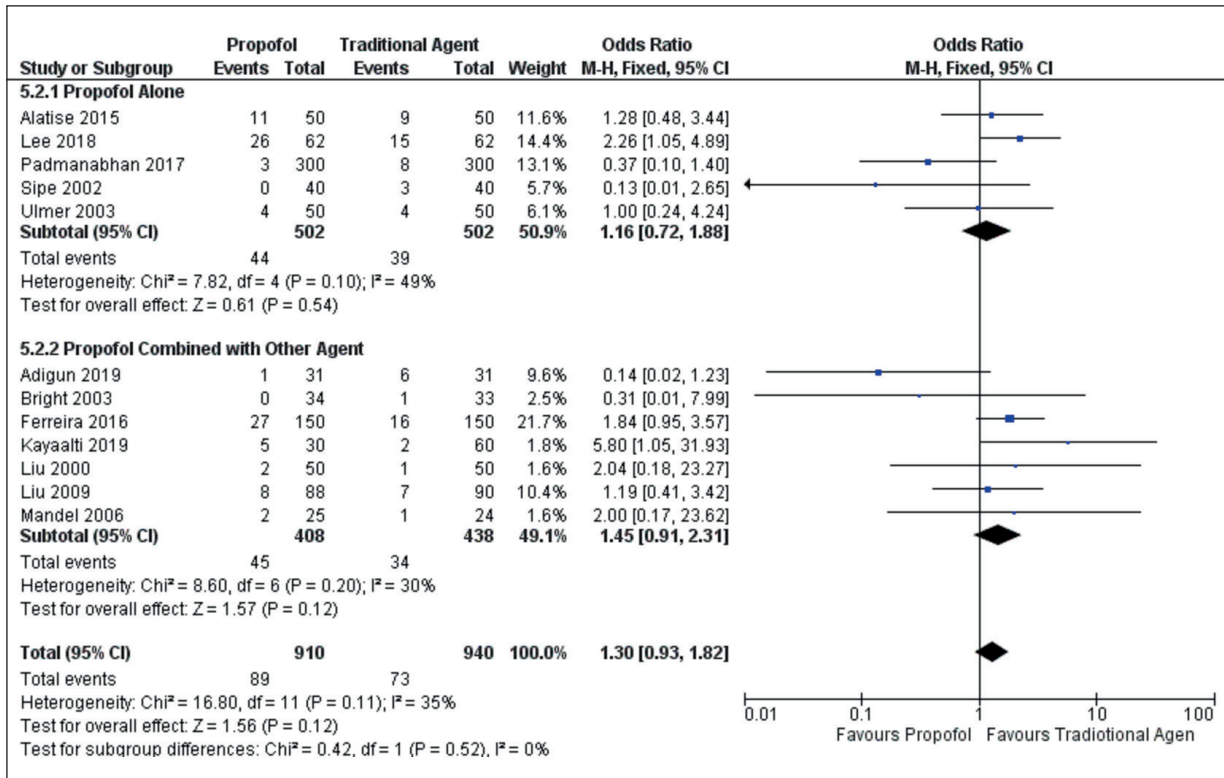


Figure 7. Forest plot comparing hypotension rates after propofol and after traditional agents.

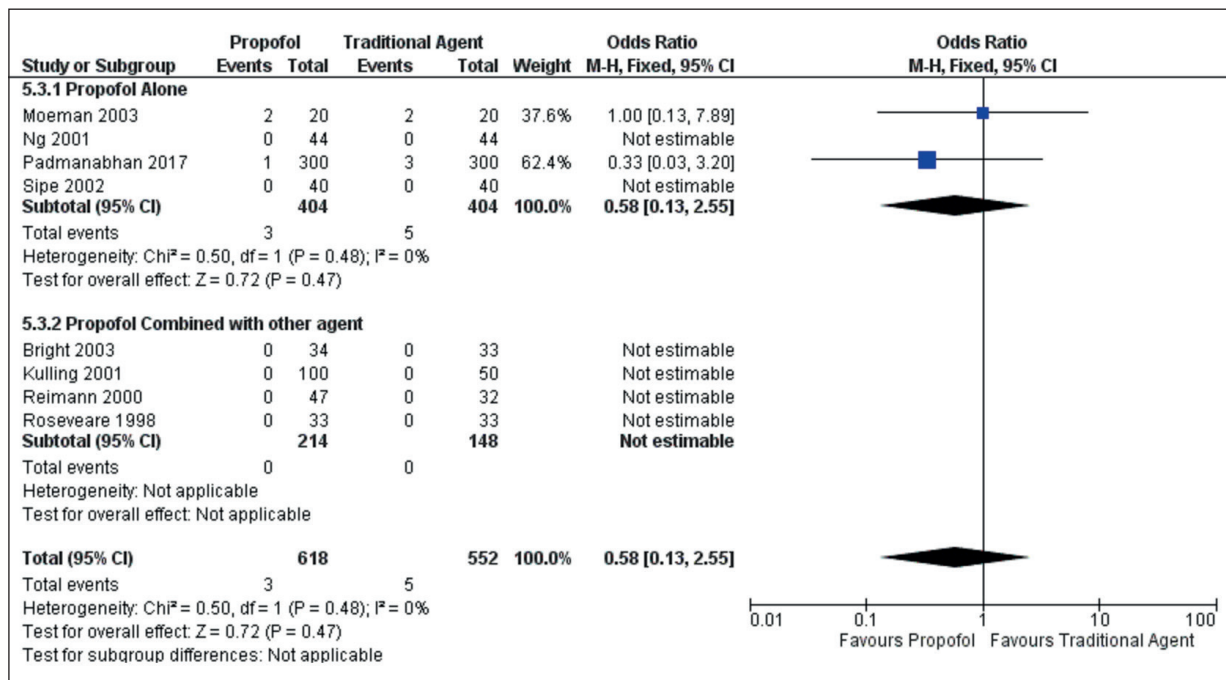


Figure 8. Forest plot comparing apnea occurrence rates after propofol and after traditional agents.

studies. Ng et al¹³, Bright et al¹⁷, Mandel et al²², and Roseveare et al²⁴ the mode of propofol delivery was by patient-controlled sedation (PCS). In the RCT by Lee et al²⁰ propofol/alfentanil was administered by PCS, while traditional sedatives were delivered intravenously in fixed doses. In the RCT conducted by Liu et al²¹, the median recovery time after propofol was 8.5 times longer than that after diazepam/pethidine sedation (16.2 min vs. 1.9 min respectively). This discrepancy may be explained by the fact that the patients in the diazepam/pethidine group remained conscious throughout the procedure²¹. Similarly, in the study by Moerman et al¹¹, the patients in the TA group were administered remifentanyl, and were awake throughout the procedure, with a mean recovery of 0 min¹¹. Taken together, these factors may contribute to the observed heterogeneity of the data.

When used alone, propofol was associated with significantly lower procedure durations than use of other agents or combinations^{10,13,14,16,17,19-22,24-27}. Six works^{19-21,24,26,27} did not report any difference in the procedure times between propofol and TA groups, while Akcaboy et al¹⁶ showed that the colonoscopy duration in the propofol group was longer than that in the TA group. Despite the heterogeneity of the data, our analysis shows a

significant reduction in procedure duration with propofol (SMD -0.28 [-0.55, -0.02], $p < 0.05$).

In this meta-analysis, we found that patients in the propofol group, were discharged quicker after the procedure^{12-15,17,23,26}. Akcaboy et al¹⁶ did not report any significant differences in the time-to-discharge. Overall, propofol led to 28.77 min shorter time-to-discharge than traditional sedatives. Moreover, patients that received propofol in combination with other agents reported even faster time-to-discharge (38.42 min difference compared to TA group) than the others^{17,23}; this may be attributed to the cumulative effects of benzodiazepine and opioid agents^{9,13,17}.

Our results show that propofol has a significantly stronger effect on the depth of sedation of the patients than traditional sedatives. Administration of propofol was associated with 1.38-fold increase in sedation scores. We showed that when administered alone, propofol led to a marked improvement of sedation depth (SMD 1.29 [0.36, 2.22], $p < 0.05$)^{13-15,27,28}. Of note, combining propofol with other agents had a slight, but insignificant effect on the sedation scores^{17,24,28,29}. This may be explained by the heterogeneity of the data.

The cecum intubation rate has been proposed as a quality indicator for colonoscopy, as lower

cecum intubation rates have been correlated with increased risk of colorectal cancer post-colonoscopy³². No consensus exists on whether deep sedation with propofol during routine colonoscopies maximizes the cecal intubation rates^{33,34}. In our analysis of 8 included RCTs, propofol-mediated sedation was associated with a slightly higher cecal intubation rate than other sedations, although the difference was not statistically significant^{13-15,17,21,23,24,30}.

Our meta-analysis evaluated the prevalence rate of the most common sedation-related adverse effects (hypotension and apnea). Any sedation during routine colonoscopy carries a risk of possible cardiorespiratory complications that are responsible for about 50% of all procedure-related deaths³⁵. In a meta-analysis conducted in 2013, Wang et al³⁶ showed that propofol use caused shorter recovery times and better sedation than traditional sedative agents, without an increase in cardiopulmonary complications. Our results agree with these observations. Although all the studies included in this meta-analysis reported data on potential adverse effects of sedation, only 8 provided results for statistical analysis of apnea^{11,13,14,17,23,24,26,30} and 12 reported data for hypotension^{10,14,15,17,18,21,22,26-28,31}. Our analysis showed that the rate of propofol-related adverse effects was similar to that of the traditional sedative agents. However, we found a slight increase in hypotension rates in patients that received propofol, this effect was not statistically significant (OR = 1.30 [0.93, 1.82]), and combination of propofol with other agents had no marked effect on hypertension rates. Propofol use was not associated with any changes in apnea occurrences (OR = 0.58 [0.13, 2.55]).

The main limitation of this study is the significant heterogeneity among the included RCTs, which may have affected our results.

Conclusions

We suggest that propofol as a sedative during routine colonoscopy significantly shortens the procedure duration and recovery times, and increases the sedation depth. Moreover, propofol reduces the time-to-discharge, when combined with other agents. Propofol may lead to a higher efficiency of the procedure without increasing the potential sedation-related adverse effects.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

KZ conceived and designed the study. KZ, HX, and HL collected the data and performed the literature search. HX were involved in data analysis. KZ was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

References

- 1) LIN OS. Sedation for routine gastrointestinal endoscopic procedures: a review on efficacy, safety, efficiency, cost and satisfaction. *Intest Res* 2017; 15: 456-466.
- 2) COHEN LB, WECSLER JS, GAETANO JN, BENSON AA, MILLER KM, DURKALSKI V, AISENBERG J. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006; 101: 967-974.
- 3) RADAELLI F, MEUCCI G, SGROI G, MINOLI G, ITALIAN ASSOCIATION OF HOSPITAL GASTROENTEROLOGISTS (AIGO). Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. *Am J Gastroenterol* 2008; 103: 1122-1130.
- 4) TRIANTAFILLIDIS JK, MERIKAS E, NIKOLAKIS D, PAPALOIS AE. Sedation in gastrointestinal endoscopy: Current issues. *World J Gastroenterol* 2013; 19: 463-481.
- 5) QUINE MA, BELL GD, MCCLOY RF, CHARLTON JE, DEVLIN HB, HOPKINS A. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. *Gut* 1995; 36: 462-467.
- 6) GRABER RG. Propofol in the endoscopy suite: an anesthesiologist's perspective. *Gastrointest Endosc* 1999; 49: 803-806.
- 7) GODSIFF L, MAGEE L, PARK GR. Propofol versus propofol with midazolam for laryngeal mask insertion. *Eur J Anaesthesiol Suppl* 1995; 12: 35-40.
- 8) BLOUIN RT, SEIFERT HA, BABENCO HD, CONARD PF, GROSS JB. Propofol depresses the hypoxic ventilatory response during conscious sedation and isohypercapnia. *Anesthesiology* 1993; 79: 1177-1182.
- 9) ZHANG W, ZHU Z, ZHENG Y. Effect and safety of propofol for sedation during colonoscopy: A meta-analysis. *J Clin Anesth* 2018; 51: 10-18.
- 10) ALATISE OI, OWOJUYIGBE AM, YAKUBU MA, AGBAKWURU AE, FAPONLE AF. Propofol versus traditional sedative methods for colonoscopy in a low-resource setting. *Niger Postgrad Med J* 2015; 22: 151-157.
- 11) MOERMAN AT, FOUBERT LA, HERREGODS LL, STRUYS MMRF, DE WOLF DJ, DE LOOZE DA, DE VOS MM,

- MORTIER EP. Propofol versus remifentanyl for monitored anaesthesia care during colonoscopy. *Eur J Anaesthesiol* 2003; 20: 461-466.
- 12) MUNOZ-NAVAS M, GARCIA-PEDRAJAS F, PANADERO A. Midazolam-flumazenil versus propofol for ambulatory colonoscopy. Preliminary results of a randomized single blinded study. *Gastrointest Endosc* 1994; 40: 29.
 - 13) NG JM, KONG CF, NYAM D. Patient-controlled sedation with propofol for colonoscopy. *Gastrointest Endosc* 2001; 54: 8-13.
 - 14) SIPE BW, REX DK, LATINOVICH D, OVERLEY C, KINSER K, BRATCHER L, KAREKEN D. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc* 2002; 55: 815-825.
 - 15) ULMER BJ, HANSEN JJ, OVERLEY CA, SYMMS MR, CHADALAWADA V, LIANGPUNSAKUL S, STRAHL E, MENDEL AM, REX DK. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003; 1: 425-432.
 - 16) AKCABOY Z, AKCABOY Y, ALBAYRAK D, ALTINOREN B, DIKMEN B, GOGUS N. Can remifentanyl be better choice than propofol for colonoscopy during monitored anesthesia care? *Acta Anaesthesiol Scand* 2006; 50: 736-741.
 - 17) BRIGHT E, ROSEVEARE C, DALGLEISH D, KIMBLE J, ELLIOTT J, SHEPHERD H. Patient-controlled sedation for colonoscopy: a randomized trial comparing patient-controlled administration of propofol and alfentanil with physician-administered midazolam and pethidine. *Endoscopy* 2003; 35: 683-687.
 - 18) FERREIRA AO, TORRES J, BARJAS E, NUNES J, GLÓRIA L, FERREIRA R, ROCHA M, PEREIRA S, DIAS S, SANTOS AA, CRAVO M. Non-anesthesiologist administration of propofol sedation for colonoscopy is safe in low risk patients: results of a noninferiority randomized controlled trial. *Endoscopy* 2016; 48: 747-753.
 - 19) KOSTASH M, JOHNSTON R, BAILEY RJ, KONOPAD E, GUTHRIE L. Sedation for colonoscopy: a double-blind comparison of diazepam/meperidine, midazolam/fentanyl and propofol/fentanyl combinations. *Can J Gastroenterol* 1994; 8: 27-31.
 - 20) LEE DWH, CHAN ACW, SZE T-S, KO CW, POON CM, CHAN KC, SIN KS, CHUNG SCS. Patient-controlled sedation versus intravenous sedation for colonoscopy in elderly patients: a prospective randomized controlled trial. *Gastrointest Endosc* 2002; 56: 629-632.
 - 21) LIU SYW, POON CM, LEUNG TL, WONG CW, CHAN YL, LEUNG TC, LEONG HT. Nurse-administered propofol-alfentanil sedation using a patient-controlled analgesia pump compared with opioid-benzodiazepine sedation for outpatient colonoscopy. *Endoscopy* 2009; 41: 522-528.
 - 22) MANDEL JE, TANNER JW, LICHTENSTEIN GR, METZ DC, KATZKA DA, GINSBERG GG, KOCHMAN ML. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentanyl versus midazolam/fentanyl for colonoscopy. *Anesth Analg* 2008; 106: 434-439, table of contents.
 - 23) REIMANN FM, SAMSON U, DERAD I, FUCHS M, SCHIEFER B, STANGE EF. Synergistic sedation with low-dose midazolam and propofol for colonoscopies. *Endoscopy* 2000; 32: 239-244.
 - 24) ROSEVEARE C, SEAVELL C, PATEL P, CRISWELL J, KIMBLE J, JONES C, SHEPHERD H. Patient-controlled sedation and analgesia, using propofol and alfentanil, during colonoscopy: a prospective randomized controlled trial. *Endoscopy* 1998; 30: 768-773.
 - 25) SCHROEDER C, KAOUTZANIS C, TOCCO-BRADLEY R, OBEAR J, WELCH KB, WINTER S, CLEARY RK. Patients prefer propofol to midazolam plus fentanyl for sedation for colonoscopy: results of a single-center randomized equivalence trial. *Dis Colon Rectum* 2016; 59: 62-69.
 - 26) PADMANABHAN A, FRANGOPOULOS C, SHAFFER LET. Patient satisfaction with propofol for outpatient colonoscopy: a prospective, randomized, double-blind study. *Dis Colon Rectum* 2017; 60: 1102-1108.
 - 27) LEE JM, MIN G, KEUM B, LEE JM, KIM SH, CHOI HS, KIM ES, SEO YS, JEEN YT, CHUN HJ, LEE HS, UM SH, KIM CD. Using etomidate and midazolam for screening colonoscopies results in more stable hemodynamic responses in patients of all ages. *Gut Liver* 2019; 13: 649-657.
 - 28) ADIGUN T, AKERE A, AYANDIPO O, AFUWAPE O. A comparison of propofol - fentanyl with midazolam - pentazocine combination for sedation and analgesia during colonoscopy in Ibadan Nigeria. *J Clin Sci* 2019; 16: 1.
 - 29) PASPATIS GA, MANOLARAKI M, XIROUCHAKIS G, PAPANIKOLAOU N, CHLOUVERAKIS G, GRITZALI A. Synergistic sedation with midazolam and propofol versus midazolam and pethidine in colonoscopies: a prospective, randomized study. *Am J Gastroenterol* 2002; 97: 1963-1967.
 - 30) KÜLLING D, ROTHENBÜHLER R, INAUEN W. Safety of nonanesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. *Endoscopy* 2003; 35: 679-682.
 - 31) KAYAALTI S, KAYAALTI Ö. Safety of applying midazolam-ketamine-propofol sedation combination under the supervision of endoscopy nurse with patient-controlled analgesia pump in colonoscopy. *World J Clin Cases* 2018; 6: 1146-1154.
 - 32) HOFF G, HOLME Ø, BRETTHAUER M, SANDVEI P, DARRE-NÆSS O, STALLEMO A, WIIG H, HØIE O, NORBERG G, MORITZ V, DE LANGE T. Cecum intubation rate as quality indicator in clinical versus screening colonoscopy. *Endosc Int Open* 2017; 5: E489-E495.
 - 33) CARDIN F, MINICUCI N, CAMPIGOTTO F, ANDREOTTI A, GRANZIAERA E, DONÀ B, MARTELLA B, TERRANOVA C, MILITELLO C. Difficult colonoscopies in the propofol era. *BMC Surg* 2012; 12: S9.
 - 34) THIRUMURTHI S, RAJU GS, PANDE M, RUIZ J, CARLSON R, HAGAN KB, LEE JH, ROSS WA. Does deep sedation with propofol affect adenoma detection rates

- in average risk screening colonoscopy exams? *World J Gastrointest Endosc* 2017; 9: 177-182.
- 35) AMORNYOTIN S. Sedation-related complications in gastrointestinal endoscopy. *World J Gastrointest Endosc* 2013; 5: 527-533.
- 36) WANG D, CHEN C, CHEN J, XU Y, WANG L, ZHU Z, DENG D, CHEN J, LONG A, TANG D, LIU J. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLoS One* 2013; 8: e53311.