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

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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, remifentanil 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 I^2 metric tests. If the I^2 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), remifentanil (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) diazemuls 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 statistically 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)

ż	Author, Year, country	Administrator	Sedation	No. of Patients	Male/ Female	Age (Mean ± SD)	Recovery Time	Time-to- Discharge	Procedure Time	Jadad score
-	Ulmer et al, 2003, Usa	Endoscopists & Nurses	Propofol Midorolom + fontonil	50	29/21	55.6 ± 11.2	16.5 ± 8.8	36.5 ± 11.9	1	5
ç	Cine of al JOOJ Ileo	Murcoo & abusiona	Mildazolam + ientanyi Demeteri	00	01/16	50.5 ± 11.8	7.01 ± C.12	40.1 ± 21.4	- 10 7 ± 5 5	~
4	Sipe et al, 2002, USa	INUISES & PILYSICIALIS	r topotot Midazolam + meperidine	40	21/19 19/21	54.2 ± 14.2	14.4 ± 0.3 33 ± 23.3	40.5 ± 19.2 71.1 ± 29.6	10.7 ± 3.3	4
e	Ng et al, 2001, Singapore	Patient controlled	Propofol	44	27/17	54 ± 15	43.3 ± 12.1	42.3 ± 12.1	8.7 ± 3.9	3
		Anesthetis	Midazolam	44	21/23	49 ± 13	61 ± 29.7	61 ± 29.7	8.7 ± 3.3	
4	Alatise et al, 2015, Nigeria	Gastroenterologist	Propofol	40	23/17	56.6 ± 12.6	I	I	22.6 ± 7.4	4
			Propofol + fentanyl + Midazolam	40	26/14	57.8 ± 11.9	I	I	28.2 ± 7.7	
Ś	Bright et al, 2003, UK	Physicians & Nurses	40 mg propofol + 1 mg alfentanil 50 mg pethidine + 2.5 mg midazolam	34 33	19/15 12/21	41.7 ± 77 54 ± 15.5	3 ± 1.7 0 ± 0	40 ± 34.5 75 ± 34.5	15 ± 7.8 15 ± 4.7	ς
9	Alkcaboy et al, 2006, Turkey	Physicians & Nurses	0.5 mg/kg propofol	50	28/22	40 (17–74)	2.1 ± 1.3	37.9 ± 9.1	22.9 ± 5.4	4
t		1 0 7 . I		49	C7/07	(0/-01) 04	1.4 ± 0.0	41./ ± 11./	10.0 H 4.0	ţ
-	Padmanabhan et al, 2017, USA	Endoscopists & Nurses	Propotol Fentanyl + midazolam	300 300	162/138 153/147	61.4 ± 9.8 61.0 ± 9.4		38 ± 6 38.5 ± 7.8	12.7 ± 3.5 13.3 ± 3.8	0
×	Moerman et al, 2003,	Nurses & physicians	1 mg/kg propofol	20	5/15	41 ± 15	3.1 ± 1.7	I	I	3
	Belgium		U.S μg/kg remirentanti	70	5/1/	40 ± 11	$U \pm U$	I	I	
6	Mandel et al, 2006, USA	Patient controlled Anesthetist	10 mg/ml propofol + 10 μg/ml remifentanil	25	13/12	60.5 ± 9.6	4 .9 ± 4 . 3	I	19 ± 9.9	б
			12.5 μg/ml fentanyl + 0.5 mg/ml midazolam	24	11/13	<i>57.7</i> ± 10.8	32 ± 25	I	21 ± 12.3	
10	Ferreira et al, 2016, Portugal	Anesthetist & Nurses	Propofol	150	61/89	58.6 ± 13.8	58 ± 33	I	I	3
			Remifentanil	127	50/77	55.4 ± 15.4	67 ± 29	I		
П	Schroeder et al, 2016, USA	Physicians & Nurses	60 mg propofol	126	65/61	57.7 ± 13.4	35 ± 7.3	I	23 ± 9.1	б
			2 mg midazolam + 50 μg fentanyl	136	76/60	58.1 ± 13.8	33.6 ± 15.0	I	24.4 ± 9.3	
12	Liu et al, 2009, China	Physicians & Nurses	4.8 mg propofol + 125 μg alfentani 0.035 mg/kg midazolam +	50	38/22 27/23	55 (43-63) 48 (35-64)	16.2 ± 4.2 1.9 ± 2.2	1 1	23.7 ± 14.4 24.2 ± 15.6	4
			0.35 mg/kg meperidine			~				
13	Roseveare et al, 1998, UK	Endoscopists & Nurses	10 mg/ml propofol + 25 μg/ml alfentanil	33	NR	52 (23-74)	10 ± 29.3	I	15 ± 5.9	7
			50 mg pethidine + 10/20 mg diazemuls	33	NR	50 (29-73)	40 ± 29.3	I	14 ± 8.3	
14	Reimann et al, 2000,	Nurses & physicians	2 mg midazolam + 20-50 mg	47	27/20	44 ± 12	5 ± 22.8	17 ± 96.6	I	б
	UCILIAILY		proportor 2 mg midazolam + 10-20 mg nalbuphine	32	17/15	41 ± 12	23 ± 22.8	93 ± 96.6	I	

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

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Table continued

ż	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 diazemuls + 0.5 mg/kg meperidine 	50 50	26/24 28/22	72.4 ± 5.3 73.5 ± 6.1	1.2 ± 1.4 6.2 ± 1.4	1 1	17.9 ± 9.9 16.8 ± 12.2	Э
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		1 1	1 1	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	7
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	1 1	7
19	Adigun et al 2019, Nigeria	Physicians & Nurses	Propofol 0.5 mg/kg with Fentanyl 0.5 ug/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	1 1	1 1	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	1 1	1 1	1 1	e
21	Kulling et al 2003, Switzerland	Physicians & Nurses	 8 mg propofol + 125 μg alfentanil 035 mg/kg midazolam + 0.35 mg/kg meteridine 	50	28/22 27/23	55 (43-63) 48 (35-64)	1 1	1 1	1 1	3
22	Lee et al 2019, Korea	Nurses	Propofol Etomidate	62 62	37/25 41/21	71.26 ± 4.53 71.37 ± 5.20	1 1	1 1	$\begin{array}{c} 29.46 \pm 16.04 \\ 29.73 \pm 12.23 \end{array}$	4

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

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Church and Carls and an	Prope	DIOI AIO	ne	Tradit	ional Ag	jent	Mainlet	Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	mean	50	Total	vveight	IV, Random, 95% CI		IV, Kandom, 95% CI
1.1.1 Propotol Alone	vs fradr	tional A	agent							
Alatise 2015	7.9	2.2	50	13.4	3.6	50	6.3%	-1.83 [-2.30, -1.36]		1
Moeman 2003	3	1.7	20	0	0	20		Not estimable		
Munoz-Navas 1994	18	12.4	14	35	12.4	15	5.9%	-1.33 [-2.15, -0.52]		1
Ng 2001	43.3	12.1	44	61	29.7	44	6.3%	-0.77 [-1.21, -0.34]		1
Sipe 2002	14.4	6.5	40	33	23.3	40	6.3%	-1.08 [-1.55, -0.61]		1
Ulmer 2003	16.5	8.5	50	27.5	16.2	50	6.3%	-0.84 [-1.25, -0.43]		1
Subtotal (95% CI)			218			219	31.1%	-1.15 [-1.55, -0.75]		
Heterogeneity: Tau ² =	0.14; CI	ni ² = 13	.25, df	= 4 (P =	0.01); P	= 70%				
Test for overall effect:	Z = 5.61	(P < 0.	00001)						
		~ **								
1.1.2 Propotol combi	ned with	Other	Agent							
Akcaboy 2006	2.1	1.3	50	1.2	0.8	49	6.3%	0.83 [0.41, 1.24]		
Bright 2003	5	29.6	34	35	29.6	33	6.2%	-1.00 [-1.51, -0.49]		1
Ferreira 2016	58	33	150	67	29	127	6.4%	-0.29 [-0.52, -0.05]		1
Kostash 1994	13.3	15.7	19	24.7	27.2	38	6.2%	-0.47 [-1.03, 0.09]		1
Lee 2002	1.2	1.4	50	6.2	1.4	50	6.1%	-3.54 [-4.18, -2.91]		2
Liu 2000	20	29.6	55	30	29.6	55	6.4%	-0.34 [-0.71, 0.04]		1
Liu 2009	16.2	4.2	88	1.9	2.1	90	6.2%	4.30 [3.76, 4.84]		•
Mandel 2006	4.9	4.3	25	32	25	24	6.1%	-1.50 [-2.14, -0.86]		
Reimann 2000	5	22.8	47	23	22.8	32	6.3%	-0.78 [-1.25, -0.32]		
Roseveare 1998	10	29.3	33	40	29.3	33	6.2%	-1.01 [-1.53, -0.50]		
Schroeder 2016	35	7.3	126	33.6	15	127	6.4%	0.12 [-0.13, 0.36]		{
Subtotal (95% CI)			677			658	68.9%	-0.33 [-1.15, 0.50]		
Heterogeneity: Tau ² =	1.89; CI	ni ² = 44	6.70, d	f= 10 (F	< 0.00	001); I ^z :	= 98%			
Test for overall effect:	Z=0.78	(P = 0.	.44)							
Total (05% CI)			00F			077	100.0%	0.501 4.24 0.041		
Total (95% CI)	4 57. 0		090			0//	070	-0.59 [-1.21, 0.04]		
Heterogeneity: Tau* =	1.57; CI	11= 51	8.77, d	IT = 15 (F	< 0.00	001); I*:	= 97%		-100	-50 0 50 100
Test for overall effect:	Z=1.84	(P = 0.	.07)				-			Favours Propofol Favours Traditional Agent
lest for subgroup diff	erences	∶Chi ^z =	3.10, (at=1 (P	= 0.08),	If = 67.	.7%			

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 $(I^2 = 99\%, p < 0.001)$. 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 timeto-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 ($I^2 = 99\%$, 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

	Pr	opofol		Tradit	ional Ag	ent	:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
3.1.1 Propofol Alone v	s Traditi	ional A	gent						
Alatise 2015	22.6	7.4	50	28.2	7.7	50	7.1%	-0.74 [-1.14, -0.33]	
Lee 2018	29.5	16	62	29.7	12.2	62	7.6%	-0.01 [-0.37, 0.34]	
Ng 2001	8.7	3.9	44	8.7	3.3	44	6.9%	0.00 [-0.42, 0.42]	
Padmanabhan 2017	12.7	3.5	300	13.3	3.8	300	9.6%	-0.16 [-0.32, -0.00]	
Sipe 2002	18.7	5.5	40	23	7.8	40	6.6%	-0.63 [-1.08, -0.18]	
Subtotal (95% CI)			496			496	37.8%	-0.28 [-0.55, -0.02]	
Heterogeneity: Tau ² = 1	0.06; Ch	i ² = 12.	27, df=	= 4 (P = (0.02); I ^z :	= 67%			
Test for overall effect: 2	Z = 2.12	(P = 0.0)	33)						
3.1.2 Propofol Combin	ed with	other l	Agent						
Akcaboy 2006	22.9	5.4	50	18.8	4.6	49	7.0%	0.81 [0.40, 1.22]	t
Bright 2003	15	7.8	34	15	4.7	33	6.3%	0.00 [-0.48, 0.48]	1
Kostash 1994	23.4	9.4	19	22.4	10.5	38	5.6%	0.10 [-0.45, 0.65]	t
Lee 2002	17.9	9.9	50	16.8	12.2	50	7.2%	0.10 [-0.29, 0.49]	
Liu 2000	25	13	55	17.6	8	55	7.3%	0.68 [0.30, 1.07]	
Liu 2009	23.7	14.4	88	24.2	15.6	90	8.3%	-0.03 [-0.33, 0.26]	
Mandel 2006	19	9.9	25	21	12.3	24	5.5%	-0.18 [-0.74, 0.38]	
Roseveare 1998	15	15.9	33	14	8.3	33	6.2%	0.08 [-0.40, 0.56]	
Schroeder 2016	23	9.1	126	24.4	9.3	136	8.8%	-0.15 [-0.39, 0.09]	
Subtotal (95% CI)			480			508	62.2%	0.16 [-0.08, 0.40]	
Heterogeneity: Tau ² = 1	0.09; Chi	i ² = 26.	24, df=	= 8 (P = 0	0.0010);	I ² = 709	%		
Test for overall effect: 2	Z = 1.28	(P = 0.1)	20)						
Total (95% CI)			976			1004	100.0%	-0.01 [-0.20, 0.18]	
Heterogeneity: Tau ² =	0.09; Ch	i ² = 52.	18, df=	= 13 (P <	0.0000	1); I ² = 7	75%		-100 -50 0 50 100
Test for overall effect: 2	Z = 0.13 ((P = 0.9)	30)						Favours Propofol Favours Traditional Agent
Test for subgroup diffe	rences:	Chi ² =	5.91, d	f=1 (P=	= 0.02),	² = 83.1	%		·

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 ($I^2 = 0\%$, 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-

	Propofe	ol Combi	ned	Tradit	ional Ag	ent		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.2.1 Propofol alone vs	Tradition	al Agent	t						
Munoz-Navas 1994	20	15.3	14	41	15.3	15	8.6%	-1.33 [-2.15, -0.52]	
Ng 2001	43.3	12.1	44	61	29.7	44	12.8%	-0.77 [-1.21, -0.34]	4
Padmanabhan 2017	38	6	300	38.5	7.8	300	15.5%	-0.07 [-0.23, 0.09]	•
Sipe 2002	40.5	19.2	40	71.1	29.6	40	12.3%	-1.21 [-1.69, -0.74]	
Ulmer 2003	36.5	11.9	50	46.1	21.4	50	13.2%	-0.55 [-0.95, -0.15]	4
Subtotal (95% CI)			448			449	62.4%	-0.73 [-1.24, -0.22]	
Heterogeneity: Tau ² = 0	.28; Chi2 =	= 34.03, 1	df = 4 (F	< 0.000	001); I ² =	88%			
Test for overall effect: Z	= 2.82 (P	= 0.005)							
2.2.2 Propofol Combine	ed with Of	ther Age	nt						
Akcaboy 2006	37.9	9.1	50	41.7	11.7	49	13.3%	-0.36 [-0.76, 0.04]	•
Bright 2003	40	34.5	34	75	34.5	33	11.9%	-1.00 [-1.51, -0.49]	•
Reimann 2000	17	96.6	47	93	96.6	32	12.5%	-0.78 [-1.25, -0.31]	•
Subtotal (95% CI)			131			114	37.6%	-0.69 [-1.07, -0.31]	
Heterogeneity: Tau ² = 0	.06; Chi ² =	= 4.17, dt	f= 2 (P :	= 0.12);	I ² = 52%				
Test for overall effect: Z	= 3.55 (P	= 0.0004	4)						
Total (95% CI)			579			563	100.0%	-0.71 [-1.06, -0.36]	
Heterogeneity: Tau ² = 0	.20; Chi ² =	= 43.56,	df = 7 (F	< 0.000	001); I ^z =	84%			
Test for overall effect: Z	= 3.98 (P	< 0.0001	1)						Favours Propofol Combined, Favours Traditional Agent
Test for subgroup differ	ences: Cl	ni² = 0.02	2, df = 1	(P = 0.8	9), I ² = 0	%			ravours rispoisi comonica Tavours nautuonarAgent

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

	Dr	onofol	6	Traditi	onal Ac	ont		Std Mean Difference	Std Mean Diff	aranca
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% Cl	IV. Random.	95% Cl
4.1.1 Propofol alone										
Adigun 2019	4.1	0.8	31	2.1	0.7	31	10.7%	2.63 [1.94, 3.32]	-	
Lee 2018	2.2	1	62	2.4	1	62	11.4%	-0.20 [-0.55, 0.15]	+	
Ng 2001	4	1.48	44	2	1.48	44	11.2%	1.34 [0.88, 1.80]		
Sipe 2002	4.7	0.6	40	3.8	1.1	40	11.2%	1.01 [0.54, 1.47]		
Ulmer 2003	4.9	0.2	50	3.6	1	50	11.2%	1.79 [1.32, 2.26]		
Subtotal (95% CI)		1.000 0000	227			227	55.7%	1.29 [0.36, 2.22]		
Heterogeneity: Tau ² =	1.05; CI	ni² = 71	8.57, df	f= 4 (P <	0.0000	1); I ² = !	95%			
Test for overall effect:	Z = 2.73	(P = 0).006)							
4.1.2 Propofol combi	ned with	Othe	r Agent	t						
Adigun 2019	4.1	0.8	31	2.1	0.7	31	10.7%	2.63 [1.94, 3.32]	-	
Bright 2003	3	2.1	34	4	2.1	33	11.2%	-0.47 [-0.96, 0.02]		
Paspatis 2002	2.7	0.5	64	2.8	0.4	56	11.4%	-0.22 [-0.58, 0.14]	+	
Roseveare 1998	2.7	0.7	33	3.2	0.8	33	11.1%	-0.66 [-1.15, -0.16]	1	
Subtotal (95% CI)			162			153	44.3%	0.29 [-0.86, 1.45]	1	
Heterogeneity: Tau ² =	1.32; CI	ni² = 6	7.30, df	f=3(P <	0.0000	1); I ² = !	96%			
Test for overall effect:	Z = 0.50	(P = 0).62)							
T. 1. 1 (0.5%) OD			000			000	100.00			
Total (95% CI)			389			380	100.0%	0.85 [0.10, 1.60]		
Heterogeneity: Tau ² =	1.27; CI	ni ² = 1	85.89, (df = 8 (P	< 0.000	01); I ² =	96%		100 -50 0	50 100
Test for overall effect:	Z = 2.21	(P = 0	1.03)						Favours Propofol Fa	vours Trad Agent
Test for subgroup diff	erences	: Chi ^z :	= 1.74.	df = 1 (P	= 0.19)	, l* = 42	.6%			

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

nea^{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 ($I^2 = 35\%$, 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]

	Drana	fal	Traditional A	t		Oddo Dotio	Oddo Botio
Study or Subarous	Propo	Total	Franciconal Ag	Total	Moinht	M U Fixed OFM CL	Odds Ratio
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
5.1.1 Propotol Alone	222		22				
Ng 2001	0	44	0	44		Not estimable	
Sipe 2002	0	40	0	40		Not estimable	
Ulmer 2003	0	50	0	50		Not estimable	
Subtotal (95% CI)		134		134		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	cable					
5.1.2 Propofol combin	ned with	other A	lgent				
Bright 2003	0	34	0	33		Not estimable	
Kulling 2001	1	100	0	50	19.5%	1.52 [0.06, 38.05]	
Liu 2009	0	88	0	90		Not estimable	
Reimann 2000	3	47	2	32	66.3%	1.02 [0.16, 6.49]	
Roseveare 1998	1	33	0	33	14.2%	3.09 [0.12, 78.70]	
Subtotal (95% CI)		302		238	100.0%	1.41 [0.34, 5.82]	
Total events	5		2				
Heterogeneity: Chi ² =	0.34, df=	2 (P =	0.84); I ² = 0%				
Test for overall effect:	Z=0.48	(P = 0.6)	(3)				
Total (95% CI)		436		372	100.0%	1.41 [0.34, 5.82]	
Total events	5		2				
Heterogeneity: Chi ² =	0.34, df =	2 (P =	0.84); $I^2 = 0\%$				
Test for overall effect:	Z=0.48	P = 0.8	(3)				U.U1 U.1 1 1U 10U
Test for subaroup diff	erences:	Not ap	olicable				Favours Propolor Favours Traditional Agent

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 ($1^2 = 0\%$, 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

	Propo	fol	Traditional A	gent		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.2.1 Propofol Alone							
Alatise 2015	11	50	9	50	11.6%	1.28 [0.48, 3.44]	
Lee 2018	26	62	15	62	14.4%	2.26 [1.05, 4.89]	
Padmanabhan 2017	3	300	8	300	13.1%	0.37 [0.10, 1.40]	
Sipe 2002	0	40	3	40	5.7%	0.13 [0.01, 2.65]	· · · · · · · · · · · · · · · · · · ·
Ulmer 2003	4	50	4	50	6.1%	1.00 [0.24, 4.24]	
Subtotal (95% CI)		502		502	50.9%	1.16 [0.72, 1.88]	◆
Total events	44		39				
Heterogeneity: Chi ² = 7	.82, df = 4	(P=0	.10); I ² = 49%				
Test for overall effect: Z	= 0.61 (P	= 0.54)				
5.2.2 Propofol Combin	ed with O	ther Ag	jent				
Adigun 2019	1	31	6	31	9.6%	0.14 [0.02, 1.23]	
Bright 2003	0	34	1	33	2.5%	0.31 [0.01, 7.99]	
Ferreira 2016	27	150	16	150	21.7%	1.84 [0.95, 3.57]	
Kayaalti 2019	5	30	2	60	1.8%	5.80 [1.05, 31.93]	
Liu 2000	2	50	1	50	1.6%	2.04 [0.18, 23.27]	
Liu 2009	8	88	7	90	10.4%	1.19 [0.41, 3.42]	
Mandel 2006	2	25	1	24	1.6%	2.00 [0.17, 23.62]	
Subtotal (95% CI)		408		438	49.1%	1.45 [0.91, 2.31]	◆
Total events	45		34				
Heterogeneity: Chi ² = 8	.60, df = 6	6 (P = 0	.20); I ² = 30%				
Test for overall effect: Z	= 1.57 (P	= 0.12)				
Total (95% CI)		910		940	100.0%	1.30 [0.93, 1.82]	◆
Total events	89		73				
Heterogeneity: Chi ² = 1	6.80, df=	11 (P =	= 0.11); I ² = 359	%			
Test for overall effect: Z	= 1.56 (P	= 0.12)				Eavours Propofol Eavours Tradictional Agen
Test for subgroup diffe	rences: C	hi² = 0.	42. df = 1 (P =	0.52), I	²=0%		ravours riopolor ravours fraulotional Agen

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

	Propo	fol	Traditional A	aent		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.3.1 Propofol Alone							
Moeman 2003	2	20	2	20	37.6%	1.00 [0.13, 7.89]	_
Ng 2001	0	44	0	44		Not estimable	
Padmanabhan 2017	1	300	3	300	62.4%	0.33 [0.03, 3.20]	
Sipe 2002	0	40	0	40		Not estimable	
Subtotal (95% CI)		404		404	100.0%	0.58 [0.13, 2.55]	
Total events	3		5				
Heterogeneity: Chi ² = 0	.50, df = 1	(P = 0	48); I² = 0%				
Test for overall effect: Z	= 0.72 (P	= 0.47)				
5.3.2 Propofol Combine	ed with of	ther ag	ent				
Bright 2003	0	34	0	33		Not estimable	
Kulling 2001	0	100	0	50		Not estimable	
Reimann 2000	0	47	0	32		Not estimable	
Roseveare 1998	0	33	0	33		Not estimable	
Subtotal (95% CI)		214		148		Not estimable	
Total events	0		0				
Heterogeneity: Not app	licable						
Test for overall effect: N	lot applica	able					
Total (95% CI)		618		552	100.0%	0.58 [0.13, 2.55]	
Total events	3		5				
Heterogeneity: Chi ² = 0	.50, df = 1	(P = 0	.48); I² = 0%				
Test for overall effect: Z	= 0.72 (P	= 0.47)				Favours Propofol Favours Traditional Agent
Test for subgroup differ	rences: N	ot appl	icable				

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 diazemuls/pethidine sedation (16.2 min vs. 1.9 min respectively). This discrepancy may be explained by the fact that the patients in the diazemuls/pethidine group remained conscious throughout the procedure²¹. Similarly, in the study by Moerman et al¹¹, the patients in the TA group were administered remifentanil, 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 timeto-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.

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