

Comparative Analysis of Intravenous Sedation Techniques in Dentistry: A Systematic Review

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Abstract

Introduction: As sedation dentistry increase in demand, the need for a gold standard becomes necessary. Several drug combinations are used to achieve optimal sedation with varied rates of success.

Aim and Objective: The aim of this study was to analyze outcomes of conscious intravenous sedation (IVS) for dental procedures.

Materials and Methods: Electronic search of the MEDLINE (PubMed) database up to April 2018 was conducted. Two reviewers independently and in duplicates identified eligible studies using specific data extraction and assessment forms. The PRISMA and MECIR guidelines were the basis for the current systematic review analyses.

Results: The search identified 567 potential publications. After review of abstracts and titles, 42 articles qualified for full-text review where seven studies satisfied the inclusion criteria allowing two analyses. The first analysis compared single versus multiple drugs showing weighted mean recovery time of 30.35 ± 4.22 min (single) versus 32.50 ± 13.50 min (multiple) and procedure time of 29.85 ± 5.18 min (single) versus 50.50 ± 20.69 min (multiple). The second analysis showed weighted mean of recovery time 12.1 ± 0.9 min; procedure time 36.8 ± 6.2 min; total dosage 255.8 ± 13.0 mg for propofol with nitrous versus recovery time 22.7 ± 8.9 min; procedure time 48.1 ± 8.6 min; total dosage 160.7 ± 15.8 mg for propofol as a single/in combination with other drugs without nitrous.

Conclusion: The recovery time and procedure length were shorter in trials using single drugs compared to multiple drugs. Further, the weighted mean showed that the use of propofol alone resulted in longer recovery time and procedure length but a lower total dosage than when combined to propofol and nitrous oxide. Despite these findings, data should be interpreted with caution due to high heterogeneity. The high number of patients in the multiple drugs compared to low number of patients in the single drug group could skew the results creating bias. Finally, definitive conclusions regarding conscious sedation cannot be made and data should be interpreted with caution due to limited number of studies.

Keywords: Anesthesia; Conscious Sedation; Dental; Nitrous Oxide, Systematic Review

Abbreviations

IVS: Intravenous Sedation; RCTs: Randomized Clinical Trials; CCTs: Controlled Clinical Trials; Prosp CTs: Prospective Clinical Trials; PRIS-MA: Preferred Reporting Items for Systematic Review and Meta-Analysis; MECIR: Methodological Expectations of Cochrane Intervention Reviews

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Introduction

Intravenous sedation (IVS) is widely used in dentistry and continues to become a popular alternative for practitioners and patients [1]. IVS provides ease of use for providers with ability to provide anxiolysis and increased comfort for patients during dental treatment [2]. Previously, IVS was primarily used by oral surgeons and dental specialists for long-spanning procedures of higher complexity and duration [1]. As technology and understanding of sedation drugs progressed, higher numbers of general practitioners adopted these techniques [3].

Conscious sedation is achieved by using one or more drugs intravenously to bring the patient to a state of reduced anxiety and awareness without complete loss of consciousness [3]. The sedation drugs provide a wide safety margin to prevent loss of consciousness, allowing the patient to respond to verbal and tactile stimulus [2]. Some of the more common drugs used among dental professionals are propofol, midazolam, diazepam and nitrous oxide with varied combinations and dosages [3]. The efficacy of sedation can be measured in a variety of ways: ability to reduce anxiety, pain sensation, and recovery time for patients are the most frequently reported objective benefits [2]. For dental providers, safety is the main concern where it is measured by oxygen saturation, procedure length, patient movement, heart rate and blood pressure [2]. Finding a combination of drugs that provides the most ideal conditions for patient is often difficult to achieve.

Aim of the Study

The aim of this study was to analyze outcomes of conscious IVS for dental procedures. Several drug combinations have been used to achieve optimal sedation with varied rates of success. This systematic review evaluated the effectiveness of IVS using one versus multiple drugs and evaluated the use of drugs with versus without nitrous oxide.

Materials and Methods

Data sources and search

An electronic database, PubMed, from 1966 to April 2018 were the basis for the current systematic review. Data collection methodology fulfilled the criteria of the Preferred Reporting Items for Meta-Analysis (PRISMA) statement [6] and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) [7]. Two reviewers (OMM and KB) conducted independent searches. Further, a hand search was conducted of bibliographies of reviews and clinical trials following the Cochrane recommendations for bias [8]. Disagreements between reviewers during data collection and quality assessment were resolved by discussion with a third reviewer (BMK).

PICO:

- Population: Adult patients in a dental school or private dental clinic.
- Intervention: Effect of intravenous sedation in dentistry.
- Comparison: The use of single drug compared to multiple drugs with or without the use of Nitrous Oxide.
- Outcome: Recovery time, procedure length and total dosage.

Study selection and interventions

Publications had to report total dosage, recovery time and duration of procedure and have the following criteria for inclusion: 1) published in English; 2) conducted on adults; 3) dental anesthesia; 4) randomized or controlled clinical trials (RCTs, CCTs) or prospective clinical trials (Prosp CTs). Exclusion criteria were: 1) did not match the inclusion criteria; 2) had missing data relevant to the systematic review.

The following search terminology was performed using Boolean operators: “anesthesia, dental”[MeSH Terms] AND (nitrous[All Fields] OR (“midazolam”[MeSH Terms] OR “midazolam”[All Fields] OR (“Conscious Sedation”[MeSH Terms] OR “Anti-Anxiety Agents”[MeSH Terms]))) AND “adult”[MeSH Terms] AND English[lang].

Data extraction and collection

A data-extraction form was developed to collect the following study information: 1) author and publication year; 2) study type and randomization; 3) treatment groups; 5) patient sample size and weight; 5) total dosage; 6) recovery time; and 7) duration of procedure. The primary study outcomes were total drug dosage, recovery time and duration of procedure:

1. Single drug versus multiple drugs.
2. Propofol with nitrous oxide versus propofol as a single drug or in combination with other drugs without nitrous oxide.

Results

The search identified 567 potential publications. After review of abstracts and titles, a total of 42 studies qualified for full text review. Seven of the 42 studies satisfied all inclusion criteria allowing two analyses to be performed (Figure 1). The seven studies had a total of 4,676 patients. All participants were classified as adults either ASA I, II or III. The studies utilized a combination or single drug administration of midazolam, propofol, and fentanyl (Table 1). All sedation procedures were carried out in an outpatient setting using intravenous sedation administration.

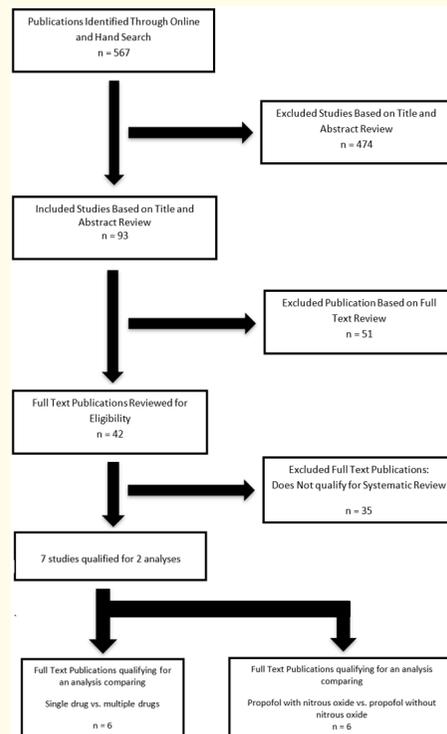


Figure 1: Flow chart for identification of publications according to PRISMA principles for systematic reviews.

Author/ Year/ reference	Study Type	Groups	Patients	ASA Status	Min Age	Max Age	Weight	Titration Level	Recovery Time	Length of Procedure
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Midazolam 1 mg	40	ASA I and II	40 ± 14 (20-85)		59 ± 12 kg (Range: 33 -102 kg)	Mean initial midazolam: 2.7 ± 0.8 mg. Range 1-7 mg. Mean total dose midazolam: 2.8 ± 0.8 mg range 1-7 mg.	15 ± 7 min (Range: 3 - 55 min)	44 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Midazolam 2 mg	354	ASA I and II	41 ± 14 (20-85)		60 ± 12 kg (Range: 33 -102 kg)	Mean initial midazolam: 2.7 ± 0.8 mg. Range 1-7 mg. Mean total dose midazolam: 2.8 ± 0.8 mg range 1-7 mg.	16 ± 7 min (Range: 3 - 55 min)	45 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Midazolam 3 mg	482	ASA I and II	42 ± 14 (20-85)		61 ± 12 kg (Range: 33 -102 kg)	Mean initial midazolam: 2.7 ± 0.8 mg. Range 1-7 mg. Mean total dose midazolam: 2.8 ± 0.8 mg range 1-7 mg.	17 ± 7 min (Range: 3 - 55 min)	46 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Midazolam 4 mg	107	ASA I and II	43 ± 14 (20-85)		62 ± 12 kg (Range: 33 -102 kg)	Mean initial midazolam: 2.7 ± 0.8 mg. Range 1-7 mg. Mean total dose midazolam: 2.8 ± 0.8 mg range 1-7 mg.	18 ± 7 min (Range: 3 - 55 min)	47 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Midazolam 5 mg	17	ASA I and II	44 ± 14 (20-85)		63 ± 12 kg (Range: 33 -102 kg)	Mean initial midazolam: 2.7 ± 0.8 mg. Range 1-7 mg. Mean total dose midazolam: 2.8 ± 0.8 mg range 1-7 mg.	19 ± 7 min (Range: 3 - 55 min)	48 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Propofol 1 mg/kg/hr	26	ASA I and II	45 ± 14 (20-85)		64 ± 12 kg (Range: 33 -102 kg)	Mean initial dose propofol: 2.5 ± 0.6 mg/kg/hr. Range 1-5 mg/kg/hr. Mean total dose propofol 132.5 ± 75.3 mg. Range: 15-530 mg	20 ± 7 min (Range: 3 - 55 min)	49 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Propofol 2 mg/kg/hr	531	ASA I and II	46 ± 14 (20-85)		65 ± 12 kg (Range: 33 -102 kg)	Mean initial dose propofol: 2.5 ± 0.6 mg/kg/hr. Range 1-5 mg/kg/hr. Mean total dose propofol 132.5 ± 75.3 mg. Range: 15-530 mg	21 ± 7 min (Range: 3 - 55 min)	50 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Propofol 3 mg/kg/hr	401	ASA I and II	47 ± 14 (20-85)		66 ± 12 kg (Range: 33 -102 kg)	Mean initial dose propofol: 2.5 ± 0.6 mg/kg/hr. Range 1-5 mg/kg/hr. Mean total dose propofol 132.5 ± 75.3 mg. Range: 15-530 mg	22 ± 7 min (Range: 3 - 55 min)	51 ± 27 min (range 1 -205 min)
Masuda, <i>et al.</i> 2017 [9]	Prospective cohort study	Propofol 4 mg/kg/hr	42	ASA I and II	48 ± 14 (20-85)		67 ± 12 kg (Range: 33 -102 kg)	Mean initial dose propofol: 2.5 ± 0.6 mg/kg/hr. Range 1-5 mg/kg/hr. Mean total dose propofol 132.5 ± 75.3 mg. Range: 15-530 mg	23 ± 7 min (Range: 3 - 55 min)	52 ± 27 min (range 1 -205 min)
Ettinger, <i>et al.</i> 2015 [10]	Retrospective cohort study	Midazolam (4.1 ± 1.1 mg) Propofol 101 ± 80 mg (Range: 1-920)	2610	ASA I, II and III	14	29		Na	46 ± 19 min (Range: 11-203 min)	30 ± 12 min (Range: 5-121 min)

Yokoe., <i>et al.</i> 2015 [11]	Randomized controlled trial	Group P: Propofol alone	44		46.6 ± 15.9	56.5 ± 10.6 kg	Total: 310.3 ± 122.4 mg	3.5 ± 2.0 min and 10.9 ± 5.6	48.3 ± 26.6 min	
Yokoe., <i>et al.</i> 2015 [11]	Randomized controlled trial	Group N+ P: Propofol + 40% Nitrous Oxide	44		42.1 ± 16.0	54.3 ± 9.8 kg	Total propofol: 249.8 ± 121.7	4.9 ± 3.1 min and 11.0 ± 6.7 min	43.5 ± 27.1 min	
Rodrigo and Jons-son 1989 [12]		Propofol	31		18	37	56 ± 2 kg (Range: 40-78 kg)	Propofol: Induction (10 mg/min) 65 ± 30 mg - Infusion 5.3 ± 1 mg/kg/h	22 ± 10 min	17 ± 4 min
Rodrigo and Jons-son 1989 [12]		Midazolam	31		18	37		Midazolam: Induction (1 mg/min) 5.5±1 mg	49 ± 22 min	20 ± 9 min
Mc-Gimpsey, <i>et al.</i> 1983 [13]		1 Midazolam (Comparative)	22	ASA I	27 ± 1.6	56 ± 1.8 kg	Midazolam 0.1 mg/kg over 1-2 min	66.5 min	18 ± 3.0 min	
Mc-Gimpsey, <i>et al.</i> 1983 [13]		2 Valium (Comparative)	18	ASA I	29 ± 1.9	60 ± 2.4 kg	0.2 mg/kg over 1-2 min	63.2 min	19 ± 4 min	
Mc-Gimpsey, <i>et al.</i> 1983 [13]		Midazolam (Open Study)	80	ASA I	30 ± 1.5	62 ± 1.2 kg		67 min	20 ± 1.4 min	
Guidon-Attali, <i>et al.</i> 1990 [14]		Propofol + 70% N ₂ O	30	ASA I	18	36	57.4 ± 9.8 kg (range: 43-85 kg)	Propofol: Induction (3.5 mg/kg) dose 207 ± 33 mg (150-300)/102.7 ± 37.7 sec (30-180) - Maintenance (9 mg/kg/h) - Total dose 261.8 ± 107.3 mg (90-565 mg)	13 ± 4 min (Range: 6-22 min)	31 ± 12 min
Lepere., <i>et al.</i> 2002 [15]	Retrospective	Surgical (42 pts) Midazolam 5.9 ± 1.9 mg, fentanyl 99.7 ± 2.8 ug, Propofol 137.2 ± 89.0 mg	85	ASA I and II	15	66	75.8 ± 15.4 kg (Range: 43-120 kg)	100 ug fentanyl with 25 ug test dose, midazolam titrated to max 5 mg ± 10 mg bolus propofol to achieve endpoint	18 min	71.4 ± 37.5 min (range 8-185 min)
Lepere., <i>et al.</i> 2002 [15]	Retrospective	Non Surgical (43 pts) Midazolam 5.9 ± 1.9 mg, fentanyl 99.7 ± 2.8 ug, Propofol 137.2 mg ± 89.0 mg	85	ASA I and II	15	66			19 ± 5.5 min	

Table 1: Characteristics of the 7 studies included in the systematic review.

The first analysis compared the use of single versus multiple drugs. Four studies met the criteria for use of a single drug [9,11-13] and two studies used multiple drugs (Table 2) [10,15]. The weighted mean recovery time was 30.35 min [SD = 4.22 (95% CI, 22.075 to 38.627; P = 0.000)] for single drug (Figure 2a) and 32.50 min [SD = 13.50 (95% CI, 6.045 to 58.964; P = 0.016)] for multiple drugs (Figure 2b). The procedure duration was 29.85 min [SD = 5.18 (95% CI, 19.683 to 40.022; P = 0.000)] for single drug (Figure 3a) and 50.50 min [SD = 20.69 (95% CI, 9.931 to 91.070; P = 0.015)] for multiple drugs (Figure 3b).

	Single Drug	Multiple Drugs
Recovery Time	30.35 ± 4.22 min	32.50 ± 13.50 min
Procedure Length	29.85 ± 5.18 min	50.50 ± 20.69 min

Table 2: Weighted mean values for first analysis comparing values of recovery time and procedure length for the use of a single drug versus multiple drugs.

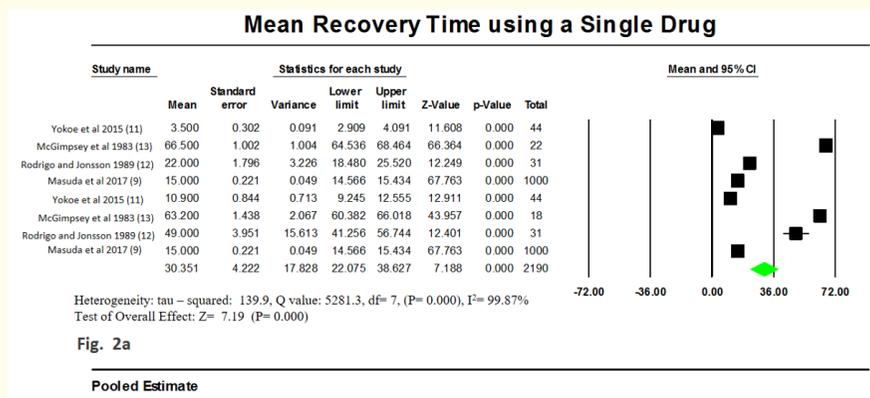


Figure 2a: Forest plot - mean recovery time using a single drug. df: Degrees of Freedom; I² = Heterogeneity.

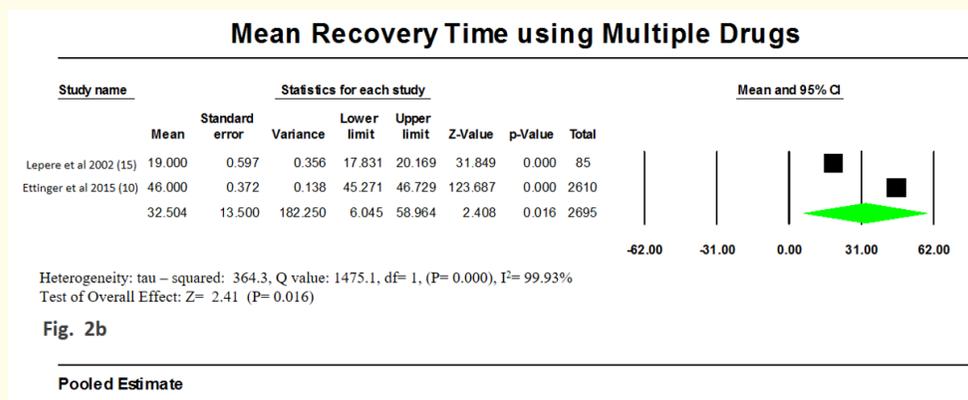


Figure 2b: Forest plot - mean recovery time using multiple drugs. df: Degrees of Freedom; I² = Heterogeneity.

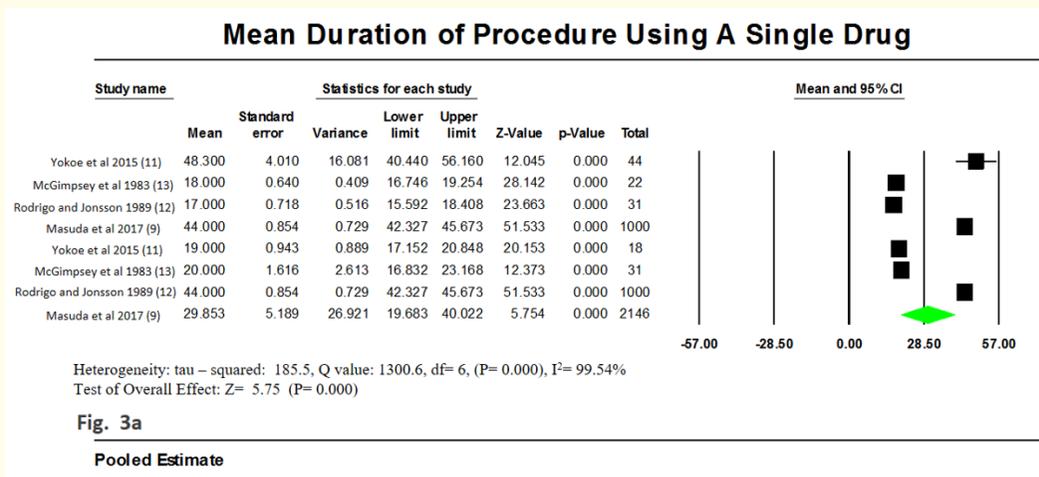


Figure 3a: Forest plot - mean duration of procedure using a single drug. df: Degrees of Freedom; I2: Heterogeneity.

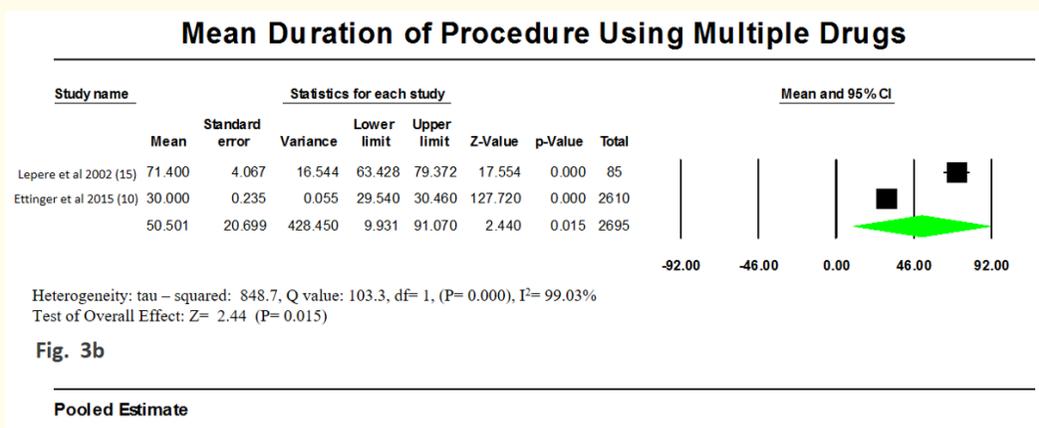


Figure 3b: Forest plot - mean duration of procedure using multiple drugs. df: Degrees of Freedom; I2 = Heterogeneity.

The second analysis compared the outcomes of procedure length, recovery time and total dosage for studies using propofol with nitrous oxide versus the use of propofol as a single drug or in combination with other drugs without nitrous oxide. Two studies (n = 74 patients) used propofol with nitrous [11,14] and four studies (n = 3,739 patients) used propofol as a single drug or in combination with other drugs without nitrous oxide [9-11,15]. The weighted mean recovery time was 12.1 min [SD = 0.9 (95% CI, 10.176 to 14.067; P = 0.000)] (Figure 4a) versus 22.7 min [SD = 8.9 (95% CI, 5.233 to 40.228; P = 0.011)] (Figure 4b); and procedure length was 36.8 min [SD = 6.2 (95% CI, 24.560 to 48.989; P = 0.000)] (Figure 5a) versus 48.1 min [SD = 8.6 (95% CI, 31.303 to 64.957; P = 0.000)] (Figure 5b); and total dosage was 255.8 mg [SD = 13.0 (95% CI, 230.223 to 281.281; P = 0.000)] (Figure 6a) versus 160.7 mg [SD = 15.8 (95% CI, 129.662 to 191.692; P = 0.000)] (Figure 6b) for propofol with nitrous oxide compared to propofol as a single drug or in combination with other drugs without the use of nitrous oxide.

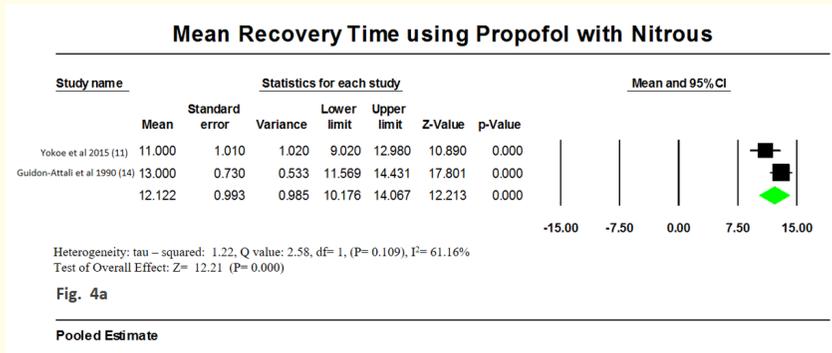


Figure 4a: Forest plot - mean recovery time using propofol with nitrous oxide. df: Degrees of Freedom; I² = Heterogeneity.

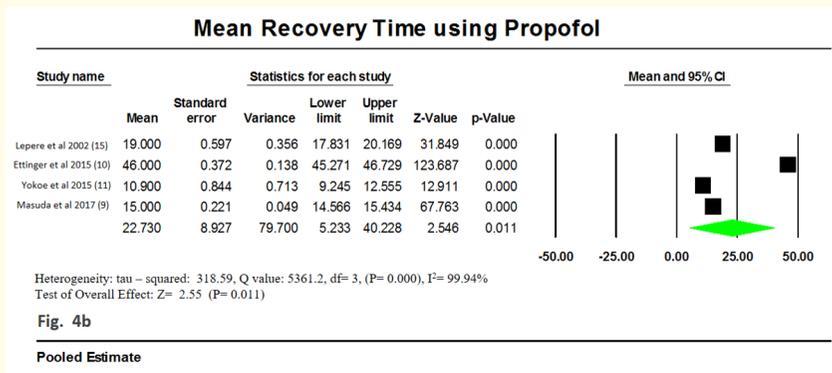


Figure 4b: Forest plot - mean recovery time using propofol without nitrous oxide. df: Degrees of Freedom; I² = Heterogeneity.

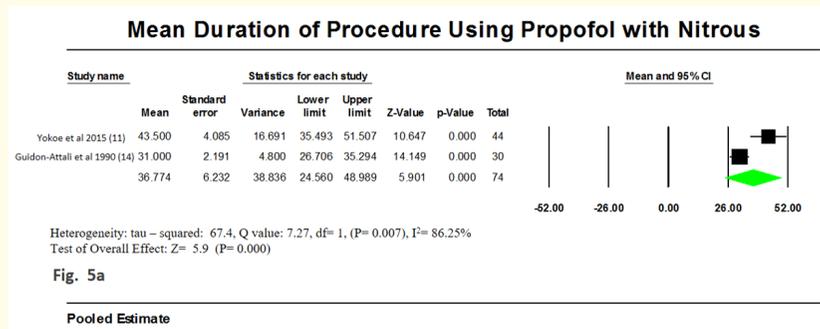


Figure 5a: Forest plot - mean duration of procedure using propofol with nitrous oxide. df: Degrees of Freedom; I² = Heterogeneity.

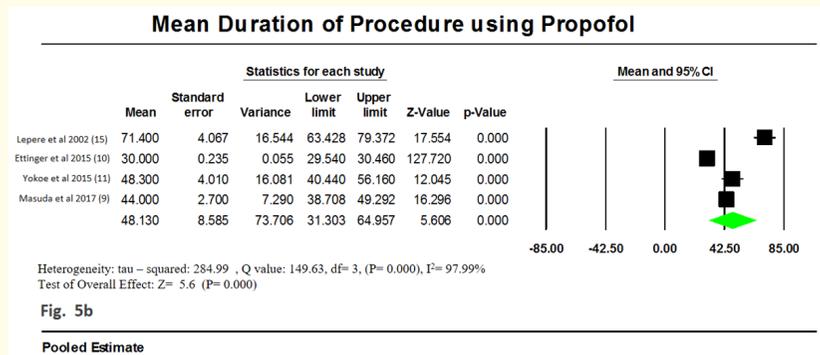


Figure 5b: Forest plot - mean duration of procedure using propofol without nitrous oxide. df: Degrees of Freedom; I² = Heterogeneity.

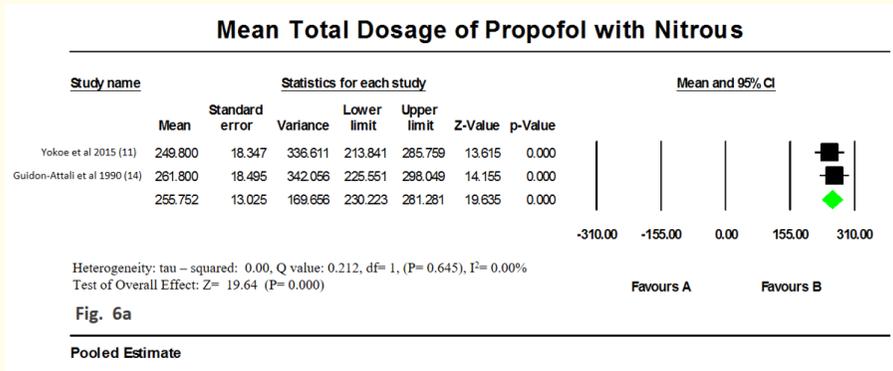


Figure 6a: Forest plot - mean total dosage using propofol with nitrous oxide. df: Degrees of Freedom; I² = Heterogeneity.

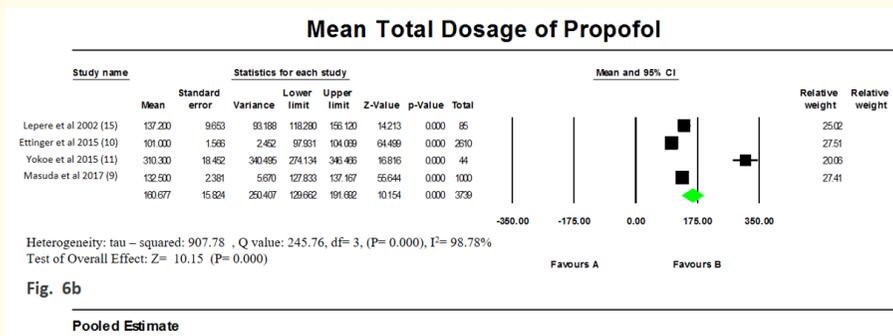


Figure 6b: Forest plot - mean total dosage using propofol without nitrous oxide. df: Degrees of Freedom; I² = Heterogeneity.

	Propofol with N ₂ O	Propofol without N ₂ O
Recovery Time	12.1 ± 0.9 min	22.7 ± 8.9 min
Procedure Length	36.8 ± 6.2 min	47.8 ± 5.9 min
Total Dosage	255.8 ± 13.0 mg	160.7 ± 15.8 mg

Table 3: Weighted mean comparison of recovery time, procedure length and total dosage for studies using propofol with nitrous oxide versus studies using propofol alone or in combination with other drugs without nitrous oxide.

Discussion

Out of all outcomes measured, statistically significant data could only be extracted from the areas of recovery time, duration of procedure and total dosage. Findings could not be evaluated with regard to amnesia, anxiolysis or hemodynamic changes. From the data we see that use of a single drug rather than multiple drugs had shorter average recovery time and procedure length, suggesting that administration of one drug intravenously is the superior method compared to use of multiple drugs.

This systematic review offers insight on the efficacy and safety of propofol alone and in combination with other drugs, with or without the use of nitrous oxide, as means for conscious sedation in the dental setting. When comparing the use of IV administered drugs in combination with nitrous oxide, we find that studies using propofol and nitrous had a significant reduction in recovery time and procedure length compared to studies that did not use nitrous. However, these studies using nitrous oxide showed an increase in total dosage of drugs needed for adequate sedation during procedures. Within each study identified in this review, there were minimal reports of adverse reactions and zero fatalities from any combination of sedation techniques. This suggests that there are several safe and reliable sedation methods that can be used in the dental outpatient setting. The analyses mentioned in this systematic review provide new information about which sedation technique has the most favorable outcome for practitioners and patients alike.

Although this review includes a relatively high number of articles compared to previous systematic reviews on the subject of IVS, there were limitations to this literature search. Due to lack of consistency among published articles in terms of data collection, several articles were not able to be used for statistical analysis. This review only offers information on use of propofol as a sedation drug due to inability to collect valuable data from many published works. There are several other drugs widely used in dental sedation that could not be properly evaluated in this study and were therefore excluded from the results. This information emphasizes the need for standardization when reporting values and findings in sedation research. In addition to inconsistencies in reported data, there were also differences within the articles eligible for review. A wide variety of procedures were performed under the sedation techniques evaluated. Case-specific parameters such as case complexity or patient health status may have contributed to a shift in data trends regarding recovery time and procedure length. Based on the evidence gathered from this systematic review, use of propofol as a single drug with simultaneous administration of nitrous oxide may be considered a superior method for conscious sedation in the dental setting. However, definitive conclusions regarding conscious sedation cannot be made and data should be interpreted with caution due to limited number of studies. More clinical further clinical trials are necessary for proper comparison of sedation drugs and their potential outcomes in the dental setting.

Conclusion

The results of this systematic review reported the following:

- The weighted mean recovery time and procedure length were shorter in trials using single drugs compared to multiple drugs.
- The high number of patients in the multiple drugs group compared to low number of patients in the single drug group could skew the results creating bias.
- The weighted mean showed that the use of propofol as a single drug or in combination with other drugs without nitrous oxide resulted in longer recovery time and procedure length but a lower total dosage than when compared to propofol with nitrous oxide.
- Despite these findings, data should be interpreted with caution as the heterogeneity was high, indicating inadequate homogeneity between the studies.
- This study revealed the need for standardization in data collection across all forms of conscious sedation research in order to generate more definitive conclusions.

Conflict of Interest

The authors declare that they have no conflicts of interest. No author received any monetary compensation for this manuscript.

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