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Review

Efficacy and cost analysis of intravenous conscious sedation for long oral surgery procedures

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Abstract

The aim of this study was to determine what is considered a long oral surgery and conduct a cost-effective analysis of sedative agents used for intravenous sedation (IVS) and sedation protocols for such procedures. Pubmed and Google Scholar databases were used to identify human studies employing IVS for extractions and implant-related surgeries, between 2003 and July/2023. Sedation protocols and procedure lengths were documented. Sedative satisfaction, operator satisfaction, and sedation assessment were also recorded. Cost estimation was based on The British National Formulary (BNF). To assess bias, the Cochrane Risk of Bias tools were employed. This review identified 29 randomised control trials (RCT), six cohorts, 14 case-series, and one case-control study. The study defined long procedures with an average duration of 31.33 minutes for extractions and 79.37 minutes for implant-related surgeries. Sedative agents identified were midazolam, dexmedetomidine, propofol, and remimazolam. Cost analysis revealed midazolam as the most cost-effective option (<10 pence per procedure per patient) and propofol the most expensive option (approximately £46.39). Bias analysis indicated varying degrees of bias in the included studies. Due to diverse outcome reporting, a comparative network approach was employed and revealed benefits of using dexmedetomidine, propofol, and remimazolam over midazolam. Midazolam, dexmedetomidine, propofol, and remimazolam demonstrated safety and efficacy as sedative agents for conscious IVS in extended procedures like extractions or implant-related surgeries. While midazolam is the most cost-effective option, dexmedetomidine, propofol, and remimazolam offer subjective and clinical benefits. The relatively higher cost of propofol may impede its widespread use. Dexmedetomidine and remimazolam stand out as closely priced options, necessitating further clinical investigations for comparative efficacy assessment.

Keywords: Intravenous conscious sedation; Long oral surgery procedures; Efficacy; Cost analysis; Dental extraction; Oral extraction; Dental implant; Oral implant; Midazolam; Propofol; Dexmedetomidine; Remimazolam

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Introduction

Conscious sedation in dental and oral surgery is considered a common technique to deliver a safe and effective treatment, by creating a supporting environment and facilities, without distress, whilst treating patients with anxiety,[1] dental or needle phobia, pronounced gag reflex, and poor cooperation,[2] as well as patients who are suffering from learning, physical, and mental disabilities.[3] Additionally, settings wherein the inherent complexity of the procedure itself (such as multiple extractions or placement of multiple implants) may benefit from sedation to mitigate patient discomfort and anxiety, ultimately enhancing overall treatment satisfaction and attenuating potential psychological effects.[4] Furthermore, the provision of sedation in these scenarios could facilitate procedural ease for the surgeon, boosting the overall operator satisfaction.[5]

It is imperative, however, to exercise caution when determining whether or not to deliver sedation. The clinician must review the patient's medical history, ensuring the safety and appropriateness of sedation, and pay attention to psychological factors that may influence the administration of sedation, such as needle phobia. Moreover, an informed consent process stands as an essential component in these cases.

The concept of long dental and oral surgery treatment

Long dental and oral surgery procedures are among the indications for conscious sedation in dentistry.[4,6] However, the existing literature does not provide clear and significant insights into what could be reasonably considered a 'long' or 'short' oral surgery treatment. Further clarification on the duration of 'long' treatments is necessary to better understand and interpret the research outcomes in this regard. A systematic review by Jamali et al (2018) studied the effect of the length of dental procedures on patients' behaviour and reviewed the difference between the long and short dental treatments.[7] The outcome of this article showed that the range of 'short' treatments varied between 15 to <30 minutes, however, the 'long' procedure could be varied, between 30 minutes and exceeding 45 minutes.[8,9] All these studies were focused on paediatric patients, and more clear definition is needed, considering the patient's factors, the extent and complexity of the procedure, and the clinician's skills and experience regarding the definition of long versus short dental treatment in adults.

Given that certain dental and oral surgery procedures may necessitate longer periods of conscious sedation due to their complexity, it would be difficult to carry out these in multiple short sessions.[10–12] Some examples include: complex restorative procedures such as full-mouth rehabilitation or extensive restorations; endodontic procedures such as root canal therapy of posterior molars with complex accessibility and root anatomy, or other surgical endodontic treatments (such as apicectomy); periodontal surgery such as flap surgery, mucogingival grafting, and crown lengthening, especially if multiple sites are being treated; oral surgery such as complex tooth/wisdom tooth extraction, surgical extraction of impacted wisdom teeth, full mouth clearance, oral implants, zygomaticus implants, block graft, sinus lifting, guided bone regeneration, and ridge split augmentation.

Rationale behind this review

The existing body of literature predominantly directs its attention towards the application of conscious sedation in oral surgery for populations involving anxious, paediatric, or special needs patients. There is little investigation on the use of sedation to improve patient comfort while mitigating potential psychological distress during long and extensive dental extraction and implant procedures. Therefore, beyond determining what is considered a long oral surgery procedure and the optimal sedative agent for such procedures, we sought to provide a comprehensive cost-benefit analysis and consideration of the financial implications of such an agent in relation to its alternatives and contribute to informed decision-making processes for both dental practices and hospitals.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed for reporting this review (Supplement-1, online only).[13] The Population, Intervention, Comparison and Outcome (PICO) framework was used to structure the reporting of eligibility criteria: Population - adult patients; Intervention - intravenous sedation (IVS) protocol in oral surgery treatment (extraction or oral implant-related procedures); Comparisons - alternative IVS protocol, placebo or no sedation; Outcomes - patient satisfaction (Primary), operator satisfaction, sedation quality assessment, and vital sign stability (Secondary).

Search strategy

PubMed and Google Scholar were the main databases used, last searched on 15 July, 2023. Supplement (1a, 1b, online only) presents the key search terms used for articles retrieval and the eligibility criteria. Study selection was conducted by two independent reviewers in two stages:

1) Initial screening of potentially suitable titles and abstracts against the inclusion criteria.
2) Screening of the full papers identified as possibly relevant to the use of IVS by at least one reviewer. In case of disagreement between reviewers, the decision was made by trying to reach a consensus or a third reviewer judged study inclusion.

Data collection

Data collection was completed independently by two reviewers. Another author reviewed extracted data and resolved any discrepancies. Relevant data for each study included: publi-

cation details (authorship, year of publication, country of origin), characteristics (demographic variables), methodology (sedation type, sedation agent, analgesic agent, doses, type, and duration of oral surgery procedure) and outcomes (sedation quality, vital signs feedback, patient, and surgeons' satisfaction). The selected studies were categorised using the Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCEBM) classification system.[14] The British National Formulary (BNF) served as the reference guide for determining the cost per average dose,[15] based on the most economical company price per agent. When a specific data point was entirely absent, we systematically documented it as 'Not Reported'. Following the data collection and analysis, we synthesised evidence narratively and graphically.

Risk of bias

The risk of bias 2 (RoB2) assessment tool was used for randomised control trials (RCTs),[16] and the risk of bias tool in non-randomised studies - of interventions (ROBINS-I) for cohort studies,[17] The bias category of 'Some concerns' was labelled as 'Moderate' for the purpose of font size clarity in the generated figures. For each study, the overall bias was given based on the highest bias score for each decision category.

Results

Fig. 1 shows the PRISMA flowchart representing study selection and inclusion.[13] Table 1 reports the studies characteristics,[5,10,11,18–63] which included 29 RCTs, six cohort studies, 14 case-series and one case-control study. Studies were classified as level of evidence II (RCTs), III (cohort studies) and IV (case-series and case-control studies). The studies primarily focused on four sedation agents: midazolam, dexmedetomidine, propofol, and remimazolam. Table 2 shows the pharmacology of the agents compared with an ideal sedative agent. Most of the included studies did not specify whether the operating surgeon acted as the person administering sedation or if a distinct clinician fulfilled the role. Only four comparative studies reported the use of sedative agents in a primary care setting [26,39,47,57] and ten studies were unclear,[18,20,21,23,27–29,34,35,54] whereas the remaining studies focused on secondary care settings.

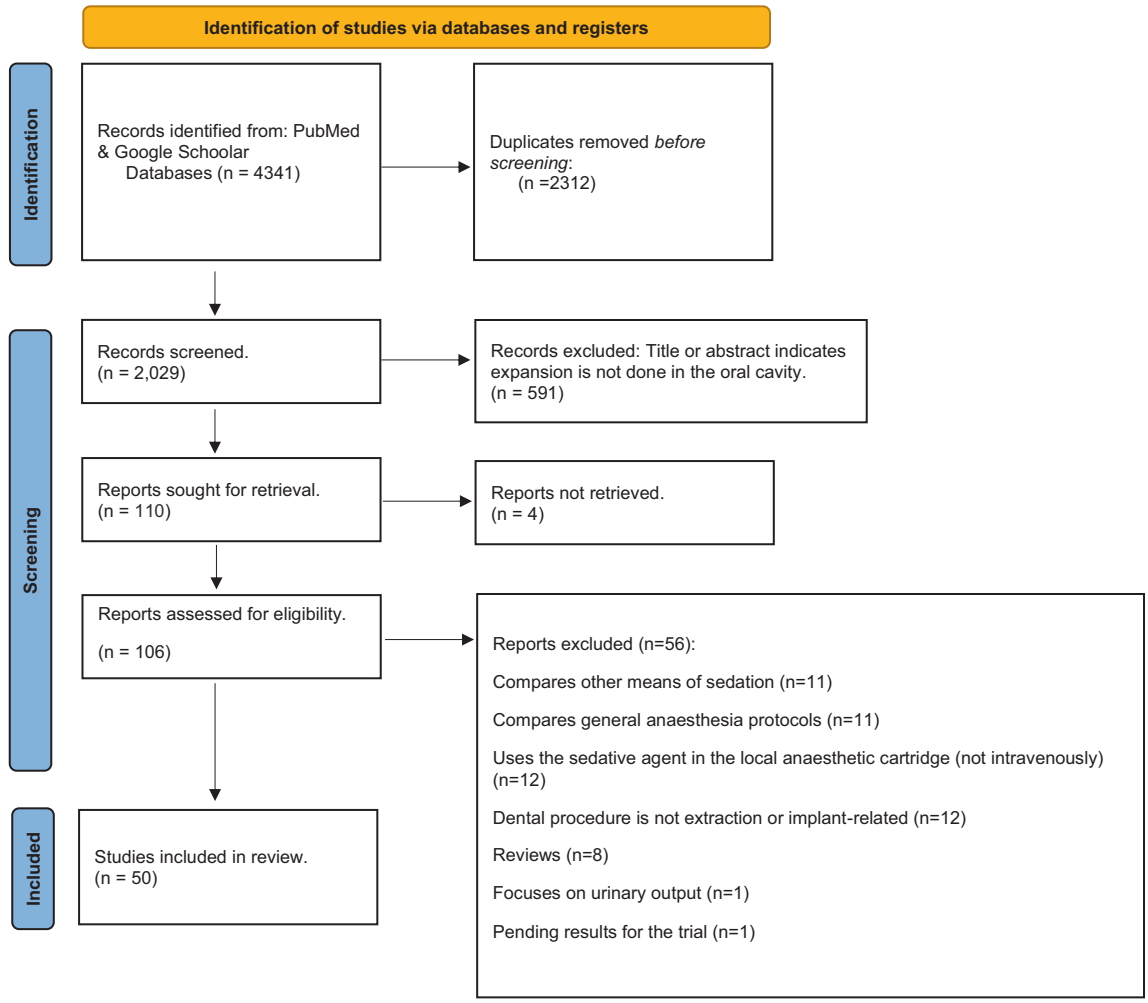

Fig. 1. PRISMA flowchart. A flowchart demonstrating the identification, screening and the inclusion process of the included articles in this review.

Table 1
Characteristics of the included studies.

First author, year, country, and reference	Study type, level of evidence and risk of bias	Population characteristics	Sedation protocol	Procedure duration	Sedative dose	Setting code
Li, 2023, China[63]	Prospective randomised controlled trial (II-moderate)	Total: 83 Male: 34 Female: 49 Age: 21.55 ± 2.20	Total: 42 Protocol: (IVS) REMIM vs Total: 41 Protocol: (IVS) MDZ	31.88 ± 1.564	MDZ = 2mg + 1mg REMIM = 5mg + 2.5mg	Secondary care
Guo, 2023, China[62]	Prospective randomised controlled, double-blind trial (II-low)	Total: 40 Male: 25 Female: 15 Age: 29 ± 4.9	Total: 20 Protocol: (IVS) REMIM + Fentanyl vs Total: 20 Protocol: (IVS) MDZ + Fentanyl	29 (14.3–44.5)	MDZ = 2.5mg REMIM = 3mg Fentanyl = 50 μg	Secondary care
Bedelo lu, 2022, Turkey[61]	Prospective randomised controlled trial (II-moderate)	Total: 140 Male: 62 Female: 78 Age: 46.50 (18–78)	Total: 69 Protocol: (IVS) MDZ vs Total: 71 Protocol: only LA	< 30	MDZ = 0.07 mg/kg	Secondary care
Zhao, 2022, China[60]	Prospective randomised controlled, single-blind trial (II-low)	Total: 100 Male: 26 Female: 74 Age: 29.75 (18–60)	Total: 50 Protocol: (IVS) REMIM + Alfentanil vs Total: 50 Protocol: (IVS) PROP + Alfentanil	28.70 ± 4.2333	Alfentanil = 0.4 μg/kg Remifentanil = 80 μg/kg + 5 μg/kg/min	Secondary care
Kim, 2022, South Korea[59]	Retrospective cohort study (III-low)	Total: 185 Male: 108 Female: 77 Age: 27.34 ± 9.15	Total: 82 Protocol: (IVS) DEX + atropine vs Total: 103 Protocol: (IVS) MDZ + pethidine	< 60	MDZ = 0.03 mg/kg/min ± 1mg DEX = 1 μg/kg + 0.5–1 μg/kg/hr	Secondary care
Guldiken, 2021, Turkey[58]	Prospective randomized controlled, double-blind trial (II-low)	Total: 43 Male: NR Female: NR Age: 53.20 ± 7.84	Total: 21 Protocol: (IVS) MDZ vs Total: 22 Protocol: (IVS) DEX	73.54 ± 24.23	MDZ = 0.03 mg/kg + 0.02 mg/kg/h DEX = 1 μg/kg + 0.5 μ/kg/h	Secondary care
Offord, 2022, UK[57]	Retrospective cohort study (III-low)	Total: 60 Male: 17 Female: 43 Age: 64 (42–79)	Total: 30 Protocol: (IVS) MDZ + PROP + Alfentanil vs Total: 20 Protocol: (IVS) MDZ + PROP vs Total: 10 Protocol: (IVS) MDZ	124.2 ± 40.2	MDZ = 11.2 ± 4 / 4.7 ± 2.6 / 4.1 ± 1.2 mg PROP = 341.0 ± 130.09 / 297.9 ± 74.5 mg Alfentanil = 726.7 ± 187.9 μg	Primary care
Uchino, 2020, Japan[56]	Prospective cohort study (III-low)	Total: 34 Male: 0 Female: 40 Age: 26.53 (20–40)	Total: 17 Protocol: (IVS) MDZ + PROP vs Total: 17 Protocol: only LA	40.32 ± 1.88	MDZ = 0.05 mg/kg	Secondary care

Wells, 2020, Australia[55]	Case-series (IV-NA)	Total: 350 Male: 115 Female: 235 Age: 28.4 ± 12.6	Total: 350 Protocol: (IVS) PROP + ALF	24.6 ± 8.4	Alfentanil = 1088 ± 228 μg PROP = -	Secondary care
Sivasubramani, 2019, India[54]	Prospective randomised controlled, double-blind Trial (II-low)	Total: 60 Male: NR Female: NR Age: (18–40)	Total: 30 Protocol: (IVS) DEX vs Total: 30 Protocol: (IVS) MDZ	NR	MDZ = 0.05 mg/kg + 0.05 mg/kg/hr DEX = 1 μg/kg + 0.5 μg/kg/hr	NR
Seto, 2019, Japan[53]	Case-series (IV-NA)	Total: 102 Male: 52 Female: 50 Age: (70–96)	Total: 102 Protocol: (IVS) DEX	44.85 ± 14.36	DEX = 2.0 to 3.1 μg/kg/hr for 10 minute	Secondary care
Hernando, 2019, Spain[51]	Case-series (IV-NA)	Total: 75 Male: 25 Female: 50 Age: 30 (23–54)	Total: 75 Protocol: (IVS) DEX	132.4 (38–294)	DEX = 0.25–1 μg/kg + 0.2–1.4 μg/kg/hr infusion	Secondary care
Togawa, 2019, Japan[52]	Prospective randomised controlled, single-blind trial (II-moderate)	Total: 88 male: 41 female: 47 age: 46 ± 15	Total: 44 Protocol: (IVS) MDZ + DEX vs Total: 44 Protocol: (IVS) MDZ + PROP	39 (25–57)	MDZ = 0.02 mg/kg DEX = 3.2–3.7 μg/kg/hr PROP = NR	Secondary care
Shin DW, 2017, South Korea[50]	Retrospective case-control study (IV-NA)	Total: 124 male: 75 female: 49 age: 26.8 (13–72)	Total: 19 Protocol: Insufficient sedation after infusion of only the initial dose of MDZ + Pethidine vs Total: 105 Protocol: Adequate sedation after infusion of the initial dose of MDZ + Pethidine	< 60	MDZ = 0.05–0.07 mg/kg * 4 times max	Secondary care
Bovaira, 2017, Spain [5]	Prospective case-series (IV-NA)	Total: 180 male: 104 female: 76 age: 50.5	Total: 180 Protocol: (IVS) MDZ + PROP + Fentanyl	92 (30–222)	MDZ = 0.05 mg/kg + 1–2 mg/h PROP = 0.3-0.5 mg/kg + 20–40 mg/h Fentanyl = 1 mg/kg + 1-2 mg/kg/h	Secondary care
Saiso K, 2017, South Korea[49]	Retrospective case-series (IV-NA)	Total: 107 male: 41 female: 66 age: 43 (9–84)	Total: 107 Protocol: (IVS) MDZ + Fentanyl	78.3 ± 38.6 (14–205 min)	Fentanyl = 66.8 ± 28.3 μg MDZ = 2.4 ± 1.7 mg	Secondary care
Almeida, 2017, Brazil[11]	Prospective cohort study (III-moderate)	Total: 30 male: 11 female: 19 age: 56.5 (43–72)	Total: 15 Protocol: GA vs Total: 15 Protocol: (IVS/OS) MDZ + Diazepam	NR	MDZ = 10mg Diazepam = 10mg	Secondary care

Kiran, 2017, India[48]	Prospective randomised controlled trial (II-moderate)	Total: 40 male: 19 female: 21 age: 28.85	Total: 20 Protocol: (IN) MDZ vs Total: 20 Protocol: (IVS) MDZ	(15–60)	MDZ = 0.1 mg/kg	Secondary care
Torun, 2017, Turkey[47]	Prospective randomised controlled, double-blind trial (II-low)	Total: 59 male: 21 female: 38 age: 23 (18–59)	Total: 29 Protocol: (IVS) Remifentanil vs Total: 30 Protocol: (IVS) Remifentanil	20 (10–45)	Remifentanil = 0.05 μg/kg + 0.05-0.1 μg/kg/min MDZ = 0.03 mg/kg	Primary care
Kumar, 2017, India[46]	Prospective randomised controlled trial (II-moderate)	Total: 10 male: 5 female: 5 age: 34.4 (14–50)	Total: 5 Protocol: (IVS) MDZ + Fentanyl vs Total: 5 Protocol: (IVS) PROP + Fentanyl	NR	PROP = 100–150 μg/kg/min Fentanyl = 2 μg/kg MDZ = 1–5 mg	Secondary care
Masuda, 2017, Japan[45]	Prospective cohort arm (IV-NA)	Total: 1000 male: 358 female: 642 age: 40.3 ± 14.3	Total: 1000 Protocol: (IVS) MDZ + PROP	44.304 ± 26.768	MDZ = 2.8 ± 0.8 mg PROP = 132.5 ± 75.3 mg	Secondary care
Brady, 2016, Ireland[44]	Case-series (IV-NA)	Total: 33 male: 11 female: 22 age: 38 ± 13 (18–63)	Total: 33 Protocol: (IVS) MDZ	NR	MDZ = 6 ± 1 mg	Secondary care
Ryu, 2016, South Korea[43]	Prospective randomised controlled trial (II-moderate)	Total: 240 male: 106 female: 134 age: 26.77 ± 6.77	Total: 80 Protocol: (IVS) DEX vs Total: 80 Protocol: (IN) DEX vs Total: 80 Protocol: LA Only	20.3 ± 10.24	DEX = 1.0 μg/kg	Secondary care
Mishra, 2016, India[42]	Prospective randomised controlled, double-blind trial (II-low)	Total: 60 male: 46 female: 14 age: 33.53 ± 10.92	Total: 30 Protocol: (IVS) DEX vs Total: 30 Protocol: (IVS) MDZ	> 60	MDZ = 0.08 mg/kg + 0.05 mg/kg/hr DEX = 1 μg/kg + 0.5 μg/kg/hr	Secondary care
Kimura, 2015, Japan[41]	Retrospective case-control study (IV-NA)	Total: 516 male: 164 female: 352 age: 61.46 ± 10.56	Total: 410 Protocol: normotensive + (IVS) MDZ + PROP + (IHS) O_2 vs Total: 106 Protocol: hypertensive + (IVS) MDZ + PROP + (IHS) O_2	38.22 ± 19.43	PROP = 1–2 mg/kg/h MDZ = 0.02–0.04 mg/kg	Primary care
McCrea, 2015, UK[6]	Prospective case-series (IV-NA)	Total: 173 male: 64 female: 109 age: 58.99 ± 12.52	Total: 173 Protocol: (IVS) MDZ	89.55 ± 34.03	MDZ = 7.677 ± 2.492 mg	Primary care

Li, 2015, China[40]	Prospective randomised controlled, double-blind trial (II-low)	Total: 60 male: 37 female: 23 age: 42.48 ± 9.15	Total: NR Protocol: (IVS) MDZ + Fentanyl vs Total: NR Protocol: (IVS) DEX + Fentanyl	61.495 ± 11.47	MDZ = 0.05mg/kg + 0.05mg/kg/hr DEX = 1.0 μg/kg + 1.0 μg/kg/hr Fentanyl = 0.001 mg/kg	Secondary care
Leach, 2015, USA[39]	Prospective randomised controlled, single-blind, cross-over trial (II-moderate)	Total: 19 male: 8 female: 11 age: 23.16 ± 5.12	Total: 19 Protocol: (IVS) DEX + PROP vs Total: 19 Protocol: (IVS) Fentanyl + PROP	10.49 ± 7.48	PROP = 50 μ/kg/min DEX = 1 μ/kg Fentanyl= 2 μ/kg	Primary care
Keerthy, 2015, India[38]	Prospective randomised controlled, double-blind trial (II-low)	Total: 40 male: 14 female: 6 age: 26.4 (20–40)	Total: 20 Protocol: (IVS) PROP vs Total: 20 Protocol: (IVS) MDZ	NR	PROP = 0.5mg/kg + 50 μg/kg/min MDZ = 75μg/kg	Secondary care
Eriksson, 2015, Sweden[37]	Prospective randomised controlled, single-blind trial (II-moderate)	Total: 87 male: 31 female: 56 age: 30.2 ± 6.8	Total: 28 Protocol: (IVS) MDZ + Tramadol vs Total: 27 Protocol: (IVS) MDZ + placebo vs Total: 32 Protocol: LA only	NR	MDZ = 11.36 ± 6.14 mg	Secondary care
Sun, 2016, South Korea[33]	Retrospective case-control study (IV-moderate)	Total: 58 male: 21 female: 37 age: 27.2 ± 10.2	Total: 25 Protocol: (IVS) PROP + Remifentanil vs Total: 33 Protocol: (IVS) PROP	66.02 ± 17.20	PROP = 163.8 ± 74.5 mg/104.3 ± 46.5 mg Remifentanil = 159.1 ± 87.9 μg	Secondary care
Brady, 2014, Canada[36]	Prospective case-series (IV-NA)	Total: 40 male: 17 female: 23 age: 21.65 (15–32)	Total: 40 Protocol: (IVS) PROP	16.7 (4–39)	PROP = 304 (110–680) mg	Secondary care
Holtzclaw, 2014, USA[10]	Retrospective case-series (IV-NA)	Total: 964 male: 446 female: 518 age: 56.49 (16–82)	Total: 964 Protocol: (IVS) MDZ + Fentanyl + (IHS) O_2 ± dexamethasone ± ketorolac	138.3 (34–390)	Fentanyl = 125.23 (25–300) μg MDZ = 9.69 (3-28) mg ketorolac = 30 mg dexamethasone = 8.24 (6–10) mg	Primary care
Wilson, 2014, USA[35]	Prospective cohort study (III-High)	Total: 54 male: 20 female: 34 age: 28.9 (18–62)	Total: 27 Protocol: (IVS) MDZ + Fentanyl vs Total: 27 Protocol: only LA	NR	MDZ = 2.5–10mg Fentanyl = up to 100 μg	NR
Smiley, 2014, USA[34]	Prospective randomised controlled, double-blind trial (II-Low)	Total: 23 male: NR female: NR age: (18–32)	Total: 12 Protocol: (IVS) MDZ + DEX vs Total: 11 Protocol: (IVS) DEX + placebo	> 30	DEX = 1 μg/kg + 0.7 μg/kg/hr MDZ = 0.03 mg/kg	NR

Kaviani, 2014, Iran[32]	Prospective randomised controlled trial (II-moderate)	Total: 33 male: NR female: NR age: 44.97 (35–60)	Total: 16 Protocol: (IVS) PROP vs Total: 17 Protocol: (IVS) MDZ	53.06	PROP = 25μg/kg/min propofol MDZ = 1mg every 2 mins untill sedation	Secondary care
Kawaai, 2014, Japan[31]	Prospective randomized controlled, double-blind trial (II-low)	Total: 40 male: 14 female: 26 age: 53.75 ± 10.76	Total: 20 Protocol: (IVS) MDZ + BUT + DEX vs Total: 20 Protocol: (IVS) MDZ + BUT + PROP	56.55 ± 14.77	MDZ = 0.05 mg/kg BUT = 0.01 mg/kg DEX = 0.56 ± 0.14 μg/kg/h PROP = 2.3 mg/kg/h	Secondary care
Yu, 2014, China30	Prospective randomised controlled, double-blind trial (II-low)	Total: 60 male: 37 female: 23 age: 33.35 ± 13.45	Total: 30 Protocol: (IVS) MDZ + Fentanyl vs Total: 30 Protocol: (IVS) DEX + Fentanyl	20.5 ± 15.2	DEX = 0.5 μg/kg + 0.5 μg/kg/h Fentanyl= 1 μg/kg MDZ = 0.05 mg/kg + 0.05 mg/kg/h	Secondary care
Yen, 2013, USA[29]	Prospective randomised controlled, single-blind trial (II-low)	Total: 59 male: 20 female: 39 age: (18–50)	Total: 32 Protocol: (IVS) FosPROP vs Total: 27 Protocol: (IVS) MDZ	38.53 (6-124)	FosPROP = 6.5 mg/kg + 1.6 mg/kg * 0-6 MDZ = 0.05 mg/kg + 0.02 mg/kg * 0-6	NR
Fan, 2013, Singapore[28]	Prospective randomised controlled, double-blind trial (II-low)	Total: 60 male: 32 female: 28 age: 27.5 ± 8.06	Total: 30 Protocol: (IVS) MDZ vs Total: 30 Protocol: (IVS) DEX	NR	MDZ = 0.005mg/kg/min + 0.01mg/kg/hr DEX = 0.1 μg/kg/min + 0.2μg/kg/hr	NR
O'Brien, 2013, UK[27]	Case-series (IV-NA)	Total: 20 male: 3 female: 17 age: 35.0 ± 14.7	Total: 20 Protocol: (IVS) (PC) PROP	25 ± 11	PROP = 1.6 ± 0.5 μg	NR
Wakita, 2012, Japan[26]	Prospective randomised controlled trial (II-high)	Total: 43 male: NR female: NR age: 51.01 (25–65)	Total: 11 Protocol: (IVS) MDZ + DEX vs Total: 10 Protocol: (IVS) MDZ + DEX vs Total: 12 Protocol: (IVS) MDZ + DEX vs Total: 10 Protocol: (IVS) DEX	NR	MDZ = 0.02-0.03 mg/kg + 0.013 mg/kg/h DEX = 1-2 μg/kg/h + 0.3-0.5 μg/kg/h	Primary care
Göktay, 2011, Turkey[25]	Prospective randomised controlled, double-blind trial (II-moderate)	Total: 60	Total: 20 Protocol: (IVS) MDZ + Tramadol vs Total: 20 Protocol: (IVS) MDZ + Fentanyl vs Total: 20 Protocol: (IVS) MDZ + saline	34.45 ± 12.28	Fentanyl = 1 μg/kg tramadol = 1mg/kg MDZ = 5.03 ± 0.99 mg	Secondary care

González-Lemonnier, 2010, Spain[24]	Prospective case-series (IV-NA)	Total: 90	Total: 90 Protocol: (IVS) MDZ + Fentanyl ± PROP ± atropine	98	MDZ = 0.05 mg/kg Fentanyl = 1 μg/kg PROP = 20-30 mg atropine = 0.01mg/kg	Primary care
Burns, 2003, Denmark[23]	Prospective randomised controlled, double-blind trial (II-low)	Total: 40 male: 31 female: 9 age: 27.3 ± 7.45	Total: 20 Protocol: (IVS) MDZ + (PC) PROP vs Total: 20 Protocol: (IVS) MDZ + PROP + placebo	27.05 ± 7.51	PROP = 129 ± 70.1 mg / 216.4 ± 52.1 mg	NR
Kwak, 2006, South Korea[22]	Prospective randomised controlled, double-blind trial (II-moderate)	Total: 40 male: 23 female: 17 age: 28 ± 10.51	Total: 24 Protocol: (IVS) PROP + Fentanyl vs Total: 16 Protocol: (IVS) PROP + Alfentanil	35.9 ± 17.06	PROP = 41.5 ± 5.9 / 50.4 ± 15.3 (μg/kg /min) Alfentanil = 7.2 ± 2.2 μg/kg Fentanyl = 1.6 ± 0.4 μg/kg	Secondary care
Juodzbalys, 2005, Lithuania[21]	Prospective cohort study (III-high)	Total: 67 male: 30 female: 37 age: (17-64)	Total: 47 Protocol: (IVS) MDZ + (IM) ketorolac vs Total: 20 Protocol: only LA	60-120	MDZ = 0.12-0.13 mg/kg ketorolac = 60mg	NR
Esen, 2005, Turkey[20]	Prospective randomised controlled, double-blind, cross-over trial (II-low)	Total: 20 male: NR female: NR age: (18–26)	Total: 20 Protocol: (IVS) MDZ + (PC) Remifentanil vs Total: 20 Protocol: (IVS) MDZ + placebo	30 (20-36)	Remifentanil = 127.3 ± 35.0 (85–200) MDZ = 0.05 mg/kg	NR
Fong, 2005, China[19]	Prospective randomised controlled, double-blind trial (II-low)	Total: 40 male: 14 female: 26 age: 27.65 ± 7.17	Total: 20 Protocol: (IVS) (PC) Remifentanil vs Total: 20 Protocol: (PC) placebo	16.25 ± 9.206	Remifentanil = 15–20 μg * 4.3±6.2	Secondary care
Ong, 2004, Singapore[18]	Prospective randomised controlled, single-blind trial (II-moderate)	Total: 117 male: 56 female: 61 age: 25.6 ± 9.71	Total: 58 Protocol: (IVS) MDZ vs Total: 59 Protocol: only LA	18.5 ± 8.9	MDZ = 5.9 ± 1.6 mg	NR

IVS = Intravenous sedation; IHS = Inhalation sedation; IN = Intranasal; IM = Intramuscular; MDZ = Midazolam; DEX = Dexmedetomidine; PROP = Propofol; FosPROP = Fospropofol, REMIM = Remimazolam; O_2 = Oxygen; LA = Local anaesthetics; NR = Not reported.

Definition of long procedure

A total of 40 studies reported procedure duration, using measures such as means, medians for central tendency, and standard deviations or ranges for data dispersion. The data yielded an average duration of 31.33 minutes for extraction procedures and 79.37 minutes for implant-related surgeries conducted under sedation. The upper limit estimates were 46.80 minutes for extraction procedures and 149.09 minutes for implant-related surgeries (Supplements -2a,-2c, online only).

Cost analysis

All 50 studies provided data on the administered doses of each sedative agent. The mean dose of each agent across all studies was computed, and the upper and lower cost bounds were established by averaging the maximum and minimum doses administered in each study. This approach was adopted in light of the heterogeneous reporting formats, involving dosage per kilogram, per kilogram per hour, per kilogram per minute, or mean dose with standard deviation (Table 3).

The presented values represent approximations of costs associated with administering a sedative agent per patient per procedure (p.pp), accounting for variations in procedure duration and patient weight. The investigation focused on four intravenous sedative agents: midazolam, dexmedetomidine, propofol, and remimazolam. Among these, midazolam emerged as the most cost-effective option, amounting to <10 pence (p.pp). Conversely, propofol was identified as the most expensive option, incurring an approximate expense of £46.39 (p.pp). Remimazolam and dexmedetomidine were found to be more closely priced (approximately £4.92 and £7.90 (p.pp), respectively) and remimazolam comparatively more economical. Administering any agent via infusion, as opposed to injection, resulted in higher costs (Fig. 2).

Table 2
Properties of intravenous sedative agents used in oral surgery.

	Ideal IVS agent	Midazolam	Propofol	Dexmedetomidine	Remimazolam
Mechanism of action	-	Acts on GABA receptor	Acts on GABA receptor	Acts on α2-adrenoceptor	Acts on GABA receptor
Anxiolysis	Yes*	Yes*	Yes*	Yes*	Yes*
Analgesia	Yes*	No	No	Yes*	No
Induction and recovery rate	Very Rapid*	Rapid	Rapid	Very rapid*	Very rapid*
Speed of change in sedation level	Very Rapid*	Rapid	Very rapid*	Very rapid*	Very rapid*
Ease of titration	Easy*	Easy*	Easy*	Easy*	Easy*
Cardiorespiratory stability	Stable*	Stable*	Stable*	Stable*	Stable*
Systemic toxicity	Low*	Low*	Moderate	Low*	Low*
Reversibility	Yes*	Reversible with flumazenil*	None	None	Reversible with flumazenil*
Injection/induction characteristics	Painless*	Painless*	Painful in small veins	Painless*	Painless*
Storage/shelf-life	Long*	3 years	3 years	2–5 years	4 years*
Distribution half-life	Short*	6-15mins	2-8 minutes	6 minutes	0.5–2 minutes*
Elimination half-life	Short*	1.5-2hrs*	2-24 hours		2.4–3.8 hours
Usual dose	-	2-7.5mg	1.5-2.5 mg/kg	0.2–1.5 μg/kg/hr	0.075–0.25 mg/kg
Late active metabolites	None*	lpha-1 hydroxy midazolam	None*	None*	None*

IVS = ; GABA = ; (-) = Not applicable, (*) = matching the property to the ideal agent.

Table 3
Costs of sedative agent per procedure.

Sedative agent	Pricing	Average dose (lower-upper bound)	Average cost (lower-upper bound)	REMIM equivalence	Cost ratio
Midazolam injection	10 x 50mg/10ml (5mg/ml) = £7.26 (AS Kalceks)	5.7 mg (3.8–8.98)	£0.07 (0.04–0.1)	0.01	1 REMIM : 100 MDZ
Remimazolam injection	10 x 20mg = £187.50 (PAION Deutschland GmbH)	5.25 mg (5.25–7.5)	£4.92 (4.92–7.03)	1.00	NA
Dexmedetomidine solution	5 x 200mcg/2ml (100mcg/ml) = £78.30 (Orion Pharma Ltd)	99.6 μg (61.37–163.17)	£7.8 (4.81–12.78)	1.66	5 REMIM : 3 DEX
Propofol injection	5 x 1% (10mg/ml) = £15.36 (Aspen Pharma Trading Ltd)	151 mg (93.13–245.47)	£46.39 (28.61–75.41)	9.82	10 REMIM : 1 PROP

MDZ = Midazolam, DEX = Dexmedetomidine, PROP = Propofol, REMIM = Remimazolam.

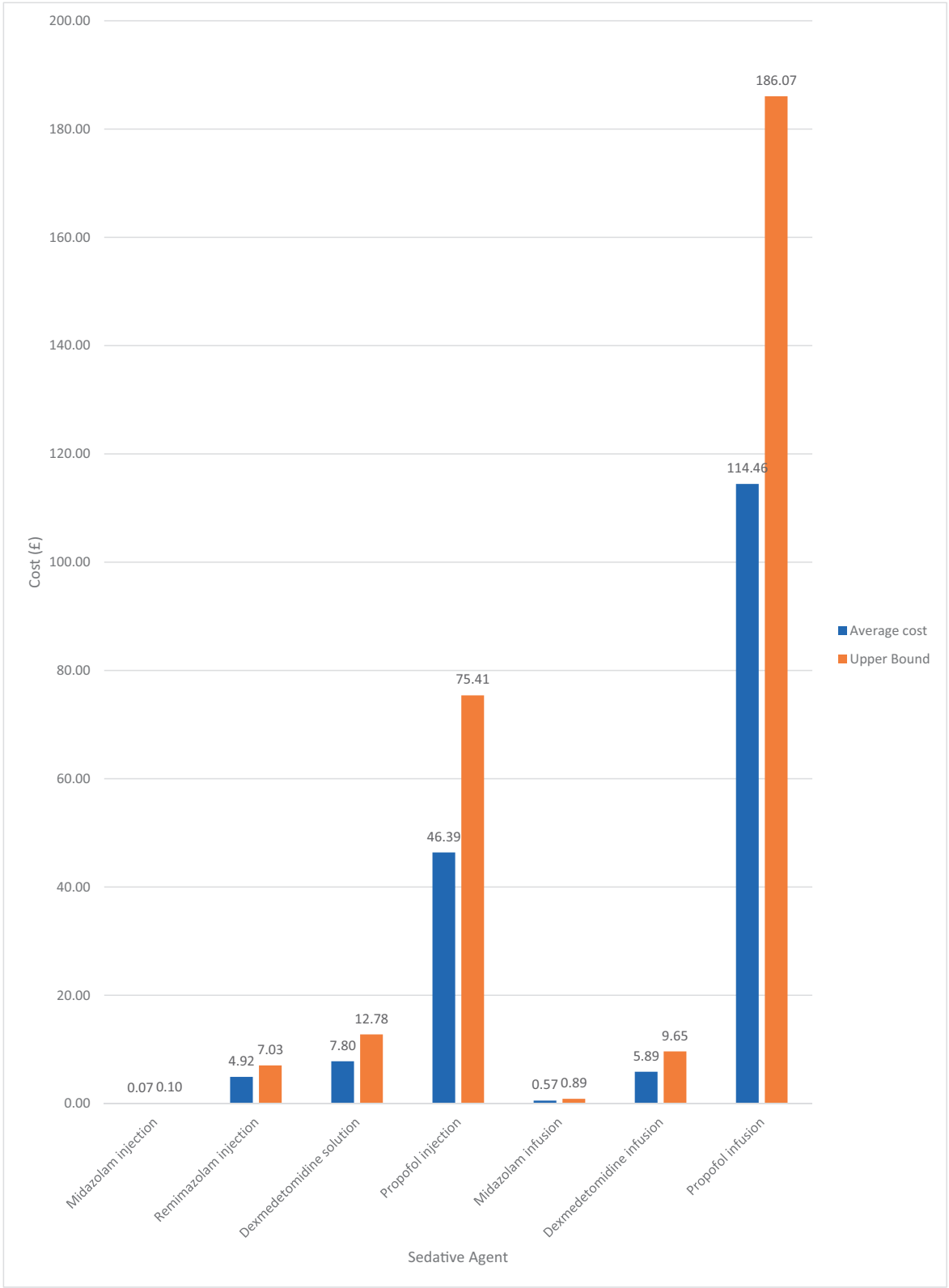

Fig. 2. Bar chart showing the average and upper costs per patient in a single extraction implant procedure. A bar chart showing the average and upper bound costs of sedative agents per patient in a single extraction on implant procedure.

Given the substantial cost advantage of midazolam over the alternative agents, remimazolam (second most affordable option) was employed to establish a cost ratio with the other agents. The cost equivalence was determined as follows: one remimazolam procedure cost equates to approximately 100 midazolam procedures, 5 remimazolam procedures costs

Fig. 3. Risk of bias and levels of evidence. A Bar chart showing the bias level within studies by their level of evidence. NA = Not Applicable.

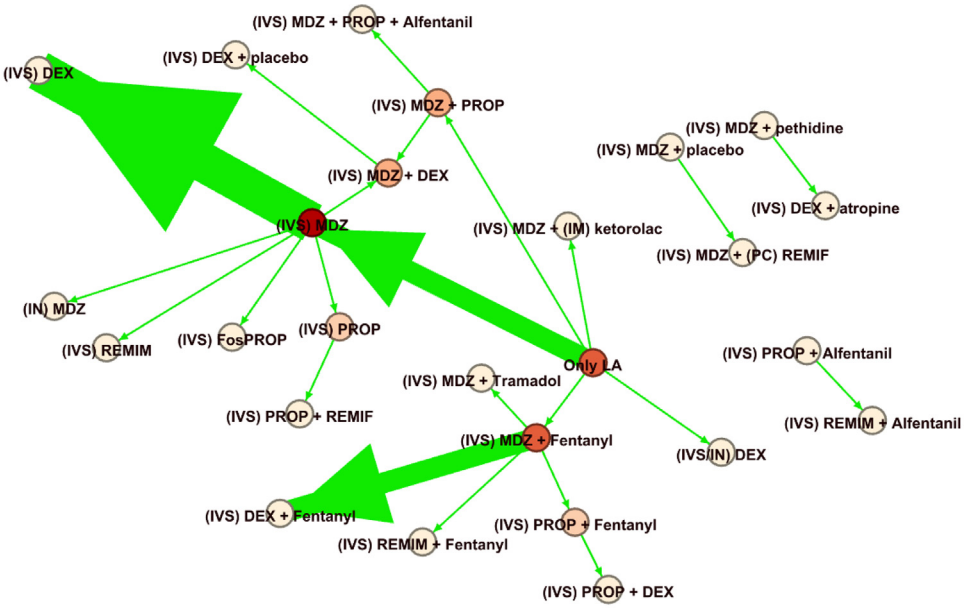

Fig. 4. Comparative network approach. A network showing the reported favoured sedation protocol per study. Legend: Edge/Connection = a study comparing two protocols, thickness represents the number of studies, node = sedation protocol, arrow points towards the favoured protocol.

equivalent to roughly two dexmedetomidine procedures, and 100 remimazolam procedures approximate the cost of one propofol procedure (Table 3).

Risk of bias

Supplement-2 displays the risk of bias results. Among the included studies, 16 out of 29 RCTs and three out of six cohort studies demonstrated a low risk of bias. The remaining articles displayed varying degrees of bias, with some showing some concerns and a few presenting a high risk (Fig. 3). Predominantly, bias risks stemmed from the absence of blinding of patients, operators, assessors, or a combination thereof.

Comparison network

Due to the high heterogeneity in outcome reporting, involving the use of varied assessment tools and questionnaires for evaluating sedation quality, patient satisfaction, and operator

satisfaction, conducting a meta-analysis was deemed unfeasible. Additionally, the range of different sedation protocols, some employing single techniques while others employ combinations, and the inclusion of opioid analgesics in certain instances, presented challenges for direct comparative analysis of many different protocols. Given this complex body of evidence (see Supplement-2c, online only), a comparative network approach was considered most appropriate (Fig. 4).

Among the comparative protocols, those involving local anaesthesia alone, midazolam as a standalone agent, and the combination of midazolam with fentanyl were the most frequently assessed against other sedation protocols. In all identified studies comparing dexmedetomidine with midazolam, dexmedetomidine emerged as the favoured option. This preference was attributed to higher levels of patient satisfaction,[54,58] shorter recovery times,[58] and lower pain scores and enhanced operator satisfaction when combined with fentanyl.[36,45] Noteworthy that dexmedetomidine administered alone yielded greater patient satisfaction than when combined with midazolam.[34]

Similarly, the comparison network illustrates a preference trend for propofol,[38,46] and remimazolam,[62,63] over midazolam in a manner parallel to dexmedetomidine. One study incorporated alfentanil and compared its combination with propofol against remimazolam, favouring remimazolam due to its shorter recovery time.[60] Another study determined that the combination of propofol and dexmedetomidine was more favourable than propofol combined with fentanyl.[39] However, no other studies made direct comparisons between propofol and remimazolam, or between propofol and dexmedetomidine. Additionally, no studies were identified that directly compared dexmedetomidine against remimazolam.

Discussion

Procedure duration

In a study by Kim et al (2014) involving 93 implant patients, it was found that approximately half of the participants believed that the treatment duration was excessively lengthy and patient satisfaction was impacted by factors related to pain.[64] In another study involving 122 elderly individuals, the most prevalent complaints revolved around the extended duration of treatment.[65] Likewise, prolonged treatment duration can have detrimental effects on staff members, encompassing physical, emotional, and personal consequences.[66] The implementation of effective strategies is crucial for clinicians to minimise potential adverse consequences associated with lengthy treatments. From this review, we acknowledged some deleterious effects on both patients and clinical staff. Effects of long procedures on patients include: physical discomfort - keeping the mouth open for prolonged periods could lead to jaw fatigue and muscle soreness; Increased anxiety - being vulnerable in the dental chair for extended periods could increase anxiety; Emotional and psychological impact - patients may experience frustration, or impatience due to the duration of the treatment. Effects on staff include: Physical and mental fatigue- physical strain from prolonged standing or maintaining uncomfortable positions; Mental strain from focusing on difficult procedures for extended periods; Emotional and psychological impact - witnessing patients in discomfort for long periods could be emotionally challenging for clinical staff, especially if they have a strong rapport with them; Increased risk of errors - maintaining a high level of precision and attention to detail throughout a lengthy treatment could be demanding, and errors may arise as a result.

Patient education regarding the treatment process, along with the provision of reassurance and support, as well as the use of effective pain management techniques, can aid in alleviating anxiety and discomfort. Therefore, conscious sedation modalities should not be considered a replacement for effective behaviour management and local anaesthesia. Nevertheless, an average of 31.33 minutes and 79.37 minutes for extractions and implant-related surgeries, respectively, were considered suitable for sedation. Our findings suggest procedures exceeding approximately 30 minutes for extraction and 80 minutes for implant-related surgeries could be considered for sedation. Re-evaluation of sedation provision for procedures of shorter duration is advised.

Given the heterogeneous reporting methods and variations in the number of extractions and implant-related surgeries across and within studies, it is imperative to regard these figures solely as estimations that offer valuable guidance for decision-making processes.

Cost of IVS

It is noteworthy that due to the different nature of procedures, varying procedure lengths, and differences in dosage administration, these figures serve as approximations rather than precise values. They are intended to offer a broad overview of the relative cost differentials among the agents. Anticipated discrepancies in costs across different countries, medical practices, and pharmaceutical companies are acknowledged. Nevertheless, the true relative differences in costs are expected to align closely with our estimations.

Bias in results

The identified absence of blinding in the studies could potentially result in inequalities in the care administered to participants across different groups, unintended differences in outcome assessment, patient expectation bias, or bias in subjectivity in how operators report their satisfaction with the sedation protocol. While the absence of blinding introduces uncertainties about the reliability and potential bias in the outcome measurements, to highlight that these concerns do not impact the calculations of procedure duration or the cost analysis.

Implications for clinical practice

For prolonged extraction or implant-related surgical procedures, the available data strongly support the safety and efficacy of midazolam, dexmedetomidine, propofol, and remimazolam as suitable sedative agents for conscious sedation. However, our cost analysis demonstrates midazolam as having a distinct economic advantage, rendering it a viable choice, particularly in settings with limited financial resources. The body of evidence identified in this review establishes that, from a clinical perspective, dexmedetomidine, propofol, and remimazolam demonstrate more favourable efficacy compared to midazolam, despite the higher costs. Moreover, the additional training required and the significantly high relative cost of propofol, when compared to the other agents, poses a challenge for its widespread adoption in clinical practice, especially in the absence of concrete evidence suggesting its clinical benefits over dexmedetomidine or remimazolam. Notably, few articles present benefits of dexmedetomidine and remimazolam over propofol.

Recommendations for future trials

Given the clinical benefits of dexmedetomidine and remimazolam over midazolam, along with their reasonable cost profiles, it is recommended that future studies direct their focus towards comparing the two agents to determine the more advantageous option. Forthcoming trials should encompass thorough reporting of key variables, including procedure duration, recovery duration, assessments of sedation quality, patient satisfaction levels, patient-reported pain, and operator satisfaction. Additionally, the inclusion of any relevant secondary outcomes would offer valuable supplementary insights. For example, while the use of sedation agents and techniques in primary and secondary care settings has been outlined in the report of Intercollegiate Advisory Committee for Sedation in Dentistry (IACSD) Standards (2020),[67] the limited clinical research dataset on primary vs secondary care setting and operator-seditionist vs seditionist only protocol, prevented to reliably assess their impact on the selection of sedative agents.

We also advocate for the use of Visual Analogue Scale (VAS) scores wherever feasible, owing to their more universally intuitive nature for both assessors and users (such as patients and operators). A uniform approach to the assessment of these variables in different clinical studies may facilitate more robust conclusions in future meta-analyses. This standardisation of assessment methodologies will contribute to a more reliable body of evidence for guiding clinical decision-making.

Limitations

To highlight that the values presented for procedure durations and cost analysis are approximate in nature, owing to heterogeneity in the reporting formats across different studies. Moreover, given the complexity involved, including the variety of agents, potential combinations among agents with or without opioid analgesics, as well as the diversity in assessment tools and study designs, the findings of this qualitative analysis may not be as robust as they would have been if a quantitative meta-analysis had been feasible.

A number of the included studies presented susceptibility to bias. However, we still opted to consider their outcomes, as they provide valuable dose, procedure duration and comparative data. This integration, while simultaneously acknowledging its inherent limitation, serves as a channel for guiding future research.

The present review strategy was not formally registered in an online repository, preventing an external verification of adherence to the intended methodology. However, it is declared with confidence that none of these methodological constraints have posed a significant influence on the overarching conclusions drawn in this review.

Conclusion

Midazolam, dexmedetomidine, propofol, and remimazolam have all demonstrated safety and efficacy as sedative agents for conscious intravenous sedation in prolonged procedures such as extractions or implant-related surgeries. While midazolam is the most cost-effective option, it is surpassed by dexmedetomidine, propofol, and remimazolam in terms of subjective and clinical benefits. The relatively higher cost of propofol compared with dexmedetomidine and remimazolam, as well as the need for special training, may limit its adoption in clinical practice, especially when there is no evidence supporting its superiority. Dexmedetomidine and remimazolam are competitively priced and hence further clinical investigations for their comparative efficacy are essential. Notably, dexmedetomidine and remimazolam are favourable when short recovery is a primary consideration.

Conflict of interest

We have no conflicts of interest.

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Ethics statement/confirmation of patient permission

No ethics approval or patient permission required for this review article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjoms.2024.04.006.

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