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Incidence of hypoxaemia with intravenous fentanyl and midazolam sedation in adult patients undergoing oral surgery procedures.

Thesis presented by

Eimear Mooney

BDS(HONS), MJDF, PGCert(Clinical Ed), PGDip(Consc Sed), FFD(OSOM)

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Cork University Dental School & Hospital

Head of School: Dr. C. Mc Creary

Supervisor: Dr. P Brady

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Abstract

Objectives

Respiratory depression and airway compromise may result in serious consequences if untreated during conscious sedation. The primary aim of this study was to investigate the incidence of hypoxaemia (SpO_2 ≤94%) in American Society of Anaesthesiologists physical status I & II patients undergoing intravenous sedation with fentanyl and midazolam. The secondary aims included determination of the onset time of hypoxaemic events and significant risk factors for hypoxaemia.

Methods

This prospective observational study required 92 patients to achieve a power of 80% at the 5% significance level. A total of 96 patients, (57 female, aged 16-65) met the inclusion criteria and consented to participation. The operator-sedationist delivered a standard dose of 50µg of fentanyl followed by titrated midazolam (range 2-9mg), at a rate no greater than 1mg/min. Oxygen saturations were monitored via pulse oximetry and supplemental oxygen was not given routinely, unless indicated. Verbal or tactile stimulation was performed to encourage respiratory effort when SpO_2 ≤94%. Monitoring continued for forty minutes from the time of sedation end point. Data were exported from the 'BeneVision N12 Mindray' monitor to Microsoft Excel. Statistical analyses (multi-variate logistical regression) were performed in SAS® (Version 9.4).

Results

All participants successfully completed treatment and 94 patients were included in the analysis. 50 (53%) individuals developed hypoxaemia, with 19 (20%) proceeding to severe hypoxaemia (SpO_2<90%). Following administration of fentanyl, 90% of hypoxaemic events occurred within 13.6 minutes; the majority (66%) were observed during the pre-operative period. The risk of hypoxaemia increased for each 1% reduction in SpO_2 and 1kPa reduction in $EtCO_2$ from baseline by 190% and 192%, respectively. The risk of moderate and severe hypoxaemia increased by 7% (p=0.0003) & 8% (p = 0.0002) respectively, for each added year of age.

Conclusions

This study presents information on the incidence of hypoxaemia for multidrug sedation in ASA I & II patients in an outpatient oral surgery department. Whilst the hypoxaemia incidence was found to be 53%, all patients remained responsive to respiratory stimulation, consistent with the definition of conscious sedation. Heightened vigilance for desaturation is required for reductions in SpO_2 and $EtCO_2$ from baseline within the first 13.6 minutes following fentanyl administration and with advancing age.

1. Introduction

Anxiety and fear remain to be one of the greatest obstacles for successful dental treatment, with 12.4% of participants identified as phobic in the 2009 adult dental health survey [(1)]. Conscious sedation has developed a reputation as an indispensable treatment modality, to facilitate successful dental treatment outcomes in anxious patients, or for surgically demanding procedures. This pharmacological behavioural management technique effectively manages anxiety in the majority of patients negating the need for general anaesthetic for many oral surgery procedures. Consequentially, the monetary value of this is easily recognisable such as reducing the pressure on hospital resources for anaesthetic teams and bed management, where short-notice cancellations due to shortages are not an uncommon inconvenience encountered by patients and their surgical team. Appropriate commissioning of resources to sedation services within oral surgery has great potential for improving access and developing our dental services.

Sedation practice in Ireland is guided by the Dental Council[(2)] who state the use of a single drug to achieve end point remote from anaesthesia as the sole technique for intravenous conscious sedation. This limits the application of advanced sedation techniques in oral surgery to only in the presence of anaesthetic cover. Ireland has a large number of specialist oral surgeons operating in primary care facilities. It may be considered a disservice to patients undergoing fear provoking and complex procedures where access to advanced sedation techniques are prohibited in the primary care environment. As a result, access to general anaesthetic in private hospitals can be difficult and surmount a significant financial burden to patients who do not have health insurance. In this regard, it may be considered that Ireland currently has a chasm of inequality in access to dental services which is a matter for commissioning bodies to address. In other jurisdictions, advanced sedation techniques have a long-standing history of being successfully and safely administered to patients who have failed to achieve anxiolysis with single drug midazolam alone, such as those with a tolerance to benzodiazepines seen in chronic anxiety states or insomniacs. Advanced techniques have a significant role in avoiding recourse to dental general anaesthetic (DGA) which is notoriously oversubscribed and largely driven by a culture of patient demand.

1.1 Support for this investigation

Standard sedation techniques have a reputable history for achieving conscious sedation successfully in adult patients. Midazolam is known to be well tolerated as a safe, predictable intravenous drug for outpatient conscious sedation procedures and possesses many properties of the ideal sedation agent. Despite many clinical reports of successful outcomes, midazolam is not proclaimed to absolutely guarantee the same level of sedation for each individual patient. Anecdotal reports describe the 'failure' of midazolam to present as a patient who may show the typical signs of sedation, alas when treatment is attempted, the patient fails to demonstrate sufficient anxiolysis. Essentially a "true" failure versus a "perceived" failure of midazolam should be distinguished to prevent a useful technique being disregarded in favour of advanced techniques. When sedation has been deemed unsuccessful with intravenous midazolam, consideration must be given to other contributing factors such as operator failure, medical and drug history and genetic variability. Failure of sedation may be attributable to poor surgical management, where a perceived failure of sedation is in fact the result of ineffective local anaesthesia. Painful stimuli will override the sedative effect of the benzodiazepine which has no analgesic potential and can result in mislabelling the encounter as a failure of midazolam rather than operator failure.

The "true" failure of midazolam has been a subject of investigation by researchers, theorizing responsibility to lie with pharmacokinetic mechanisms. One such mechanism postulated to contribute to the variable individual responsiveness to benzodiazepines includes genetically determined variations in GABA receptors, resulting in some individuals being relatively less sensitive. Benzodiazepines act on different receptors to fulfil sedative and anxiolytic effects, via the GABA receptor complex in the cerebral cortex and the glycine receptor complex in the brainstem respectively. Increasing the midazolam dose does not directly parallel with increases in each of these clinical effects and thus can potentially give rise to the sedated patient who still claims to anxious about treatment. Predicting the likelihood of successful sedation with midazolam would be very useful for clinical decision making. Predictive factors that may require consideration include the medication history, concurrent liver or renal disease and blood albumin levels. As yet, there is no decision making tool available to help clinicians navigate these decisions, with much being determined by clinical experience. Fentanyl and midazolam have been reserved for cases of single drug sedation failure, whether or not these have been a true failure remains unknown as these cases are scantly reported.

There is a void in the dental evidence base for defining the incidence of hypoxaemia with combined opioid and benzodiazepine sedation specific to the dental environment. Much of the published literature is derived from the medical specialties involved in procedural sedation, such as gastroenterology. As the occurrence of adverse events in dental sedation are rare, hypoxaemia may be considered a surrogate measure for complications. Avoidance of hypoxaemia, prompt recognition and management to correct oxygen saturations can help prevent development of untoward outcomes such as cardiac and cerebral ischaemia.

The potent combination of fentanyl and midazolam can result in a significant depression of the physiological respiratory responses, with increased risks for developing hypoxaemia and apnoea[3]. The synergistic action of opioids and benzodiazepines has been investigated by Ben-Schlomo[4] for the induction of anaesthesia. Midazolam was determined to be eight times more potent in the presence of an opioid, illustrating the synergistic action between these drug types. Similarly Vinik et al. [5] demonstrated a significant dose-dependent reduction in the hypnotic ED50 (effective dose for 50% of patients) when midazolam and alfentanil were combined.

There is no report in the dental evidence base as yet, quoting the incidence of hypoxaemia observed with combined intravenous fentanyl and midazolam for oral surgery procedures in the absence of routine supplemental oxygen delivery to the sedated patient. Neither has there been an attempt to identify the most likely time when a hypoxaemic event is most likely to occur. Previous procedural sedation research has attempted to delineate risk factors for hypoxaemia, but as yet they remain poorly defined in the dental environment. Dentists are trained in conscious sedation to take precautions in monitoring patient oxygenation. To be 'forewarned is forearmed', therefore defining the observed incidence of hypoxaemia with the synergistic combination of fentanyl and midazolam, along with the most likely onset time in the dental department creates potential for more astute monitoring. The dental sedationist can more precisely monitor oxygen saturations clinically and execute punctual interventions to prevent hypoxaemia and the potential for ensuing complications.

1.2 Guideline development for advanced sedation techniques

The last twenty years have seen multiple published standards and guidelines relating to the practice of conscious sedation by various stakeholders. These guidelines were more recently amalgamated and reviewed by a collaboration of bodies, renamed as the Intercollegiate Advisory Committee on Sedation in Dentistry (IACSD) [6]. In 1990, recommendations were made to reduce the risk of death or adverse events occurring during dental treatment culminating in publication of 'The Poswillo Report' [7]. This was implemented across NHS regional health authorities to varying degrees, triggering a number of changes. Consequentially, a report was delivered from the Chief Medical and Dental Officers in England, titled 'A Conscious Decision' [8] which ultimately led to cessation of general anaesthesia in primary dental care. General anaesthetic was hence reserved to only within hospital environments where there would be access to critical care facilities. Within this report the provision of conscious sedation procedures was endorsed for delivery by a trained operator-sedationist with support from an appropriately trained assistant.

The dental community acknowledged a deficiency in defining the acceptable minimal standard for training in advanced sedation techniques in dentistry prompting a report from the Standing Committee on Sedation for Dentistry in 2007, 'Standards for Conscious Sedation in Dentistry: alternative techniques" [9]. This built on earlier guidance provided by "Conscious Sedation in the Provision of Dental Care", produced by the Standing Dental Advisory Committee in 2003 [10] and was the first document to inform practitioners of the minimum standard required for safe and effective clinical care for the application of 'alternative conscious sedation techniques'. This document was specific to the dental profession only and reviewed the evidence on the safe application of sedation services and provided recommendations relevant to the requirements for training and practice.

In 2010 the National Institute for Health and Clinical Excellence (NICE) commissioned the document "Sedation in Children and Young People" [11] as a result of the developing changes in sedation services to children accompanied by an increased demand. Two broad aims were outlined, firstly to review the evidence regarding efficacy and safety of common drug techniques and secondly, to form a consensus view on what resources were necessary for a sedation service. There was emerging evidence that

large numbers of children in the UK were undergoing single or repeated procedures with considerable variation in treatments provided.

The Academy of Medical Royal Colleges (AoMRC) updated their guidance in 2010 "Safe sedation practice for healthcare procedures"[12] due to evolving sedation and clinical procedures in line with an older population with accompanying co-morbidities. This guidance was directed at all medical and dental specialties involved in the delivery of procedural and conscious sedation. A key recommendation from this document was 'competency based' formal training for all involved in the delivery of sedation. The AoMRC recommended the order in which opioids and benzodiazepines should be administered when utilized in combination, "the opioid should be given first and the benzodiazepine only given once the peak effect of the opioid is observed".

The first edition of 'Standards for Conscious Sedation in the Provision of Dental Care' produced in 2015 by the IACSD [13] has made one of the most significant contributions to conscious sedation guidelines in recent times. The committee consists of the four Dental Faculties of the Royal Colleges of Surgeons and the Royal College of Anaesthetists. The intention of this document was to replace all other preceding guidelines. It has been acknowledged for developing improvements in regulating sedation due to the recommendations on more consistent, validated training with ongoing continued professional development and audit.

Regarding 'standard' and 'advanced' sedation, the IACSD recommend the choice of technique to be individualised to the patient's needs, adopting a policy of minimum intervention. This advocates for the simplest and safest technique to be selected which is most likely to be effective for the patient following thorough pre-assessment. Specifically, advanced techniques "should only be considered by those skilled in their use where there is clear clinical justification, after having excluded simple techniques and must only be used in an approved setting where team skills are sufficient to resuscitate and stabilise a patient until the arrival of the emergency services". The importance of competency is discussed with regard to the sedationist who must be competent in the technique used, along with the requirement for validated skills of the other team members in caring for the patient. The use of a small dose of opioid followed by titrated midazolam is considered suitable for the operator-sedationist

in primary care, providing that the sedationist and second appropriate person have successfully completed recognised training programmes, obtained an appropriate level of experience and that only ASA I & II adults (>16 years) are treated.

Following publication of the IACSD standards, common themes of uncertainty began to emerge creating confusion regarding compliance with the document and consequently led to difficulties among those concerned with the commissioning of sedation services. In light of this, the Scottish Dental Clinical Effectiveness Programme (SDCEP) responded to the request of the UK Chief Dental Officers and applied their rigorous methodology, collaborating with TRiaDS (Translation Research in a dental setting) and accredited by NICE. The updated SDCEP guidance in 2017 [(14)] was aimed to be more user friendly with practical guidance on the provision of conscious sedation.

The key recommendation listed in the SDCEP guidance on advanced sedation techniques is based on level 4 evidence. Considering the additional risk accompanying these techniques where drug combinations have less predictable effects than single drugs, advanced techniques should only be employed if the clinical needs of the patients are not suited to the standard technique. The SDCEP guidelines provided further clarity on the personnel involved in providing advanced sedation techniques, reiterating the fundamental principle of healthcare professionals working within their competency. Concern arose from interpretation of the IACSD guidelines among the dental profession regarding the need for competence in 'age-appropriate' rescue procedures. SDCEP clarified that medical and dental staff may already have these skills, there is no need for practitioners to have broader anaesthetic skills which are not directly relevant to the administration of conscious sedation in dentistry. For advanced techniques, both SDCEP and IACSD concur that the sedation team must have immediate access to the skills and facilities similar to an NHS acute trust for prompt recognition and management of adverse incidents.

For certain advanced techniques, a dedicated sedationist is required for sedation with ketamine, sevoflurane, propofol (target-controlled infusion), propofol with midazolam as well as other techniques considered as advanced for children or young people. Provision of these techniques will

have a significant impact for training to ensure the team have the relevant knowledge and skills, with the appropriate equipment and facilities.

The code of practice relating to conscious sedation that is currently upheld by the Dental Council in Ireland considers anything other than single drug sedation to require the same precautions as general anaesthesia [2]. The Dental Council states that the sedation technique should be "limited to the use of one sedative drug with a single titrated dose and an end point remote from anaesthesia". The use of multi-drug techniques are restricted, "more than one sedative drug must not be considered simple sedation and would require the same precautions as for the administration of a general anaesthetic". This curbs the practice of advanced sedation techniques in specialty primary care practice and some dental hospital services in Ireland, where access to facilities capable of providing general anaesthesia with accompanying critical care and expertise are not readily available.

1.3 Essential qualifications and training requirements

Both regulatory authorities including the Irish Dental Council and General Dental Council (UK) emphasise the need for dental professionals to work within the limits of their knowledge, skills, training and experience. The SDCEP guidelines provide clear definitions regarding child, young person and adult, as well as outlining the differences between standard and advanced sedation techniques (Figure 1).

Child	A person under 12 years of age[6,8]
Young person	A person aged 12 – 16 years[6]
Adult	A person aged 16 years or over[6]
Standard sedation techniques*	Also known as 'basic' techniques. Includes: • For a child, young person or adult, inhalation sedation with nitrous oxide/oxygen and • For a young person or adult, midazolam by any route (intravenous, oral or transmucosal)
Advanced sedation techniques*	Also known as 'alternative' techniques. Includes: • For a child, young person or adult: o certain drugs used for sedation (e.g. ketamine, propofol, sevoflurane); o combinations of drugs used for sedation (e.g. opioid plus midazolam, midazolam plus propofol, sevoflurane plus nitrous oxide/oxygen); o combined routes of administration (e.g. oral plus intravenous)[6,8] and • For a child, midazolam by any route

Figure 1: Definitions relating to patients and sedation techniques[(14)].

The terms 'standard' and 'advanced' in relation to sedation techniques were proposed by the Independent Expert Group on Training Standards for Sedation in Dentistry (IEGTSSD) who delivered a syllabus for training requirements for medical and dental practitioners preparing to use advanced techniques for adult patients [(15)]. The IEGTSSD outlined the entry requirements to training in advanced techniques, acknowledging the different education and training backgrounds (Figure 2).

REQUIREMENTS FOR ENTRY TO TRAINING IN ADVANCED CONSCIOUS SEDATION TECHNIQUES IN DENTISTRY*

1. **ESSENTIAL**

- A primary registrable dental or medical qualification
- Not less than 4 years post-registration experience in the UK as a dental or medical practitioner
- Possession of the knowledge, skills, attitude, behaviour and aptitude compatible with the delivery of basic conscious sedation techniques
- Evidence of having undertaken training in basic sedation techniques
- Documented experience of basic sedation techniques (at least 100 cases over last 2 years), including patient outcomes
- Compliance with GMC/GDC CPD requirements
- Compliance with contemporary standards for the provision of basic conscious sedation techniques
- Evidence of regular training in Immediate Life Support or equivalent

2. **DESIRABLE**

- A postgraduate dental qualification (e.g. MFDS/MFGDP, MSc/Diploma/Certificate in sedation)
- A postgraduate medical qualification (e.g. FRCA)
- Experience of delivering training in conscious sedation for dentistry

*Anaesthetists holding a CCT and possessing documented evidence of completion of equivalent training in conscious sedation for dentistry under the auspices of the Royal College of Anaesthetists approved training programme (2010) are exempt.

Figure 2: Requirements for entry to training in advanced conscious sedation techniques in dentistry[15].

For the first time, a national standard detailing the syllabus of education and training requirements for all members of the dental sedation team was provided by the IACSD. All providers of sedation training courses including deaneries and those out-with universities are now required to apply for accreditation by the IACSD. To prepare for independent practice a minimum clinical experience in supervised practice is required to achieve competency in standard and advanced techniques, combining an opioid and benzodiazepine (Table 1).

Table 1: Requirements for clinical sedation techniques[6].

	Initial theory and skills training	Additional theory and skills training	Recommended minimum clinical experience in monitored practice to achieve competency (number of cases appropriate to age group)	Life support training for all team members	Other rescue measures (vi)	Monitoring (in addition to clinical)*	Operator-sedationist (with second appropriate person)	Dental nurse training (viii)	Environment (primary = 1; secondary = 2) (ix)
Nitrous oxide / oxygen (i)(ii)	Y	N	10	ILS PILS	Resp dep Airway		Y	CDSN / equivalent	1/2
Midazolam, intravenous (i)(ii)	Y	Adults: N Paeds: Y	20	ILS PILS	Resp dep Airway	NIBP Pulse oximetry	Y	CDSN / equivalent	1/2
Temazepam, oral (i)(ii)	Y	Adults: N Paeds: Y	10	ILS PILS	Resp dep Airway	NIBP Pulse oximetry	Adults: Y Paeds: N/A	CDSN / equivalent	1/2
Midazolam, oral (i)(ii)	Y	Adults: N Paeds: Y	10	ILS PILS	Resp dep Airway	NIBP Pulse oximetry	Y	CDSN / equivalent	1/2
Midazolam, intranasal (i)(ii)	Y	Adults: N Paeds: Y	10	ILS PILS	Resp dep Airway	NIBP Pulse oximetry	Y	CDSN / equivalent	1/2
Opioid + midazolam (i)(ii)(iii)	Y	Y	20	ILS PILS	Resp dep Airway	NIBP Pulse oximetry (Cap) (vii)	Adults: Y Paeds: N	CDSN +	Adult: 1/2 Paeds: 2

Practitioners involved in the delivery of conscious sedation are required to engage in relevant continued professional development[16]. The IACSD recommends that in order for revalidation, each member of the sedation team should engage with a minimum of twelve hours of CPD in each five-year cycle, relevant to the technique practiced.

1.4 Pharmacology

Where the use of a single agent has been unsuccessful in achieving an adequate degree of sedation, the combination of an opioid and benzodiazepine is one of the most frequently used alternatives to avoid resorting to general anaesthesia. Opioids have a less intense and more unpredictable effect than sedative anxiolytics. However the synergistic action of the combination of these two drug families is well documented. It remains to be known that there is no single perfect drug to satisfy all the sedation requirements for one particular patient.

BENZODIAZEPINES

Benzodiazepines rapidly diffuse across the blood-brain barrier and exert their mechanism of action on the central nervous system (CNS) via the $GABA_A$ (gamma aminobutyric acid) receptor complexes consisting of α-, β-, and γ subunits owing to their shared common core ring structure. GABA is an inhibitory neurotransmitter, released from presynaptic nerve endings and binds to cell membrane receptors on the postsynaptic neurone. The benzodiazepine receptor is located on the γ subunit of the $GABA_A$ receptor facilitating an influx of chloride ions once activated, hyperpolarising the cell membrane and increasing the threshold for firing an action potential. The result is a reduction in transmitted sensory messages perceived by the brain. Benzodiazepines act to potentiate the inhibitory effects of endogenous GABA resulting in sedation, anxiolysis, muscle relaxation, amnesia and anticonvulsant effects. Clinical effects exerted by benzodiazepines include anxiolysis, anterograde amnesia, muscle relaxation, anti-convulsant, hypnosis, reduction in cerebral blood flow, cerebral metabolism, systolic and diastolic blood pressure, vascular resistance, tidal volume and respiratory rate[17].

Midazolam

Midazolam was first synthesised by Hoffman-La Roche in 1975 with more clinically appealing properties than other parenteral preparations of benzodiazepines such as diazepam. It has a well-established reputation for safety and is used effectively in conscious sedation through careful intravenous titration.

Physical properties

Midazolam is a water-soluble benzodiazepine due to the substitution of imidazole at the 1,2 position on the 1,4-benzodiazepine ring structure. This removes the need for coupling with potentially irritating solvents removing the painful sensation and preventing phlebitis sequalae at the site of intravenous injection. Once administered, midazolam becomes lipophilic at physiological pH, allowing for rapid distribution in the CNS and adipose tissues. Multiple routes of administration are possible including intravenous (IV) , intramuscular (IM), oral, intranasal (IN) and rectal.

Pharmacokinetics and biotransformation

The clinical onset of action can be observed within one to two minutes owing to the highly lipophilic nature allowing the drug to reach the receptor sites quickly. Midazolam is approximately 96% bound to serum albumin. The duration of sedation will be influenced by the relatively long elimination half-life (1.8-6.4 hours), a large volume of distribution including adipose tissue and a rapid plasma clearance.

The α– half life (distribution and redistribution) is between 4- 18 minutes and the β-half life (metabolism and excretion) is 1.7 to 2.4 hours, which equates clinically with a short duration of action and a rapid inactivation and excretion of the drug which is appealing to ambulatory sedation procedures.

Midazolam undergoes hepatic metabolism by oxidation into three major metabolites (α–hydroxymidazolam, 4-hydroxymidazolam and α,4-hydroxymidazolam) which are not pharmacologically active, proving advantage for outpatient conscious sedation. The water-soluble metabolites undergo glucuronide conjugation and are excreted via the kidneys.

Pharmacodynamics

The use of Midazolam in conscious sedation is heralded for its powerful anterograde amnesia which has been shown to be superior to other benzodiazepines[18]. Amnesia is most profound immediately after induction with some disturbance to short term memory observed for several hours. The amnesic effect is not guaranteed and can vary considerably between patients.

Slow intravenous titration of midazolam in the doses used for conscious sedation in ASA I & II patients has little effect on the dynamics of the cardiovascular and respiratory systems. In contrast these systems can potentially be affected in elderly or systemically unwell cohorts. Ventilatory mechanisms can be depressed as a result of relaxation of the muscles of respiration creating a reduction in tidal volumes and respiratory rate. Impaired sensitivity of central and peripheral chemoreceptors to carbon dioxide and oxygen impairs the capacity of the central respiratory network to increase respiratory drive in the presence of hypercarbia &/or hypoxia. There are few significant cardiovascular effects of midazolam in healthy patients. A reduction in vascular resistance and mean arterial pressure with concomitant reduction in stoke volume is usually compensated by the baroreceptor reflex therefore it has negligible clinical significance unless pre-existing cardiovascular disease is present.

Dosage

Midazolam should be delivered in a slow, titrated manner according to the patient response. Case selection may determine the initial bolus which can be 2mg in healthy ASA I & II adults, but reduced to 1mg or less in elderly patients. Further 1mg doses may be given at one-minute intervals until the clinical end point is observed such as a delayed reaction to verbal commands, slurring of speech, relaxed demeanour and half-way ptosis of the upper eyelid [19]. Rapid intravenous administration can create a respiratory suppression to the point of apnoea even in young, healthy individuals.

Paradoxical reactions

Occasionally instead of the desired sedative and tranquil effects, midazolam can precipitate disinhibition, disorientation, inconsolable crying, agitation and restlessness which are all reversible with flumazenil[20].

Pre-assessment considerations and cautions

A thorough pre-assessment prior to midazolam sedation should determine the following:

- Allergy or hypersensitivity to benzodiazepines
- Acute pulmonary insufficiency
- Respiratory depression
- Hypoalbuminaemia: As midazolam is highly protein bound, a reduction in serum albumin concentration can lead to greater sedative effects.
- Elderly: Reduced clearance of midazolam in elderly populations implies caution should be exercised, with reduced dose increments titrated slowly.
- Hepatic impairment: The high clearance rate of midazolam is partly dependent on the hepatic blood flow rate which will be prolonged in presence of hepatic impairment.
- Renal impairment: A larger proportion of midazolam will be present unbound in patients with renal impairment due to a reduction in the concentration of serum albumin, allowing for greater pharmacodynamic effect.
- Repeated administration of the drug can saturate adipose tissue followed by redistribution to the blood and potential for a hangover effect.

Drug interactions

Concomitant administration of midazolam with cytochrome P450 inhibitors can result in a greater depth of sedation, occurring with azole antifungals, macrolide antibacterials and grapefruit juice. The resultant pharmacokinetic effects are slower metabolism and excretion.

Relationship between pharmacokinetic parameters and pharmacodynamic effects

The level of sedation that is achieved with midazolam has been shown to correlate with the level of receptor binding, achievable with a wide range of midazolam blood levels. Patients who show a reduced sensitivity to midazolam may be as a result of differences in receptor density, as observed with alcoholics. The pharmacokinetics do not explain why the elderly population display a greater sensitivity, nor the hysteresis between the plasma concentration of midazolam and the effect on the CNS.

A lengthy period of sedation may potentially arise with protracted administration of midazolam allowing for accumulation of the drug and active metabolites in adipose tissue where it may be slowly released. This may be most readily demonstrated in patients with renal impairment but can also be observed in those with normal renal function.

Flumazenil

Immediate access to the agonist flumazenil is a pre-requisite to commencing midazolam sedation. The use of flumazenil is a marker of over-sedation and was previously described as a 'never event' by the IACSD guidelines along with failure to monitor oxygen saturations. The updated guidance from IACSD now classifies only one never event for conscious sedation i.e. 'mis-selection of high strength midazolam during conscious sedation'. The Rapid Response Report[21] aligns with IACSD, advising that the use of flumazenil should be audited on the basis that its administration is only indicated for use in an over sedated patient. However in special care dentistry, flumazenil has beneficial applications in more challenging patients with learning disability or physical impairments where it can assist in recovery, enabling the patient and escort to be discharged from the outpatient premises more safely

Flumazenil is a competitive antagonist with a greater affinity for the benzodiazepine receptors and will completely displace midazolam from the receptor sites. It has no effect on the permeability of the cell membrane to chloride ions resulting in the restoration of normal neuronal conduction activity.

Physical properties

Water soluble at low pH.

Supplied in aqueous solution at a concentration of 0.1mg/ml in 5ml ampoule.

Pharmacokinetics and biotransformation

More than 50% of flumazenil is plasma protein bound resulting in sufficient unbound drug for rapid distribution. Hepatic metabolism produces inactive metabolites which are excreted via the kidneys. The elimination half-life is about one hour, which may be prolonged in elderly patients.

Pharmacodynamics

The sedative and anxiolytic effects of midazolam will be reversed with low doses of flumazenil. Higher doses are required to reverse the anti-convulsant effects of midazolam[22]. However the anterograde amnesic properties are not affected[23].

Re-sedation

The differing elimination half-lives of midazolam and flumazenil (1.5-3 hours and 1 hour respectively) raised concerns regarding the potential for re-sedation. For a patient to return to the same level of sedation prior to administration of the antagonist, the residual midazolam would have to competitively replace flumazenil at the receptor sites as the plasma concentration of flumazenil reduces. However when consideration is given to the time elapsed from point of midazolam delivery before flumazenil administration, as well as the re-distribution and elimination half-lives of midazolam which continues to be displaced, the effects of midazolam will also decline in tandem with the elimination half-life of flumazenil. This typically corresponds with the time most patients would be expected fit for discharge after a single dose of midazolam[24]. Birch and Miller failed to find any evidence of clinical signs of re-sedation when flumazenil was delivered as a 0.5mg bolus to reverse the acute effects of intravenous midazolam[25].

Pre-assessment considerations and cautions

Where a patient's regular medication includes benzodiazepines, such as a control medication for epilepsy, a reversal can result in seizure activity[26].

Contra-indications

Reported hypersensitivity or allergy to benzodiazepines.

Recommended reversal of midazolam:

Rapid reversal can lead to sympathetic stimulation, nausea, vomiting, headaches and dizziness and so careful titration will allow for partial rather than complete reversal to achieve a co-operative patient, capable of following verbal commands.

The elective reversal regime for a titrated dose of midazolam is generally accepted as:

1. Initial dose of 0.2mg over 15 to 30 seconds
2. Followed by increments of 0.1mg at 1 minute intervals[22].

OPIOIDS

Opioids mediate their agonistic action at the mu, kappa and delta (μ, κ, and δ) opioid receptors in the CNS. Therapeutic effects include analgesia, sedation and euphoria. Opioids are “cardioprotective”, reducing catecholamine release and obtund sympathetic reflexes to noxious stimuli, therefore are particularly beneficial for patients with hypertension, tachyarrhythmias and ischaemic heart disease.

The putative benefits of incorporating opioids in sedation is justified mainly on an empiric basis. The sedative effects of opioids are synergistic with most sedatives and the analgesic effect may reduce the discomfort associated with local anaesthetic injections. The CNS depressant effects of this multi-drug technique must be borne on mind, using the lowest possible doses for the shortest duration.

Fentanyl

Fentanyl is an opioid agonist with no intrinsic anxiolytic or amnesic properties, most commonly used in combination with midazolam to achieve conscious sedation with a rapid-onset and short-duration of action.

Physical properties

Fentanyl, N-(1-phenethyl-4-piperidyl) is structurally similar to meperidine and is available as fentanyl citrate in a water soluble, white crystalline powder that does not require preservative. May be administered via IV, IM neuraxial transdermal, transmucosal and by inhalational routes.

Dosage

The recommended dosage of fentanyl is predicated on the patient receiving another CNS depressant. The local protocol in Cork University Dental School & Hospital is to deliver an initial bolus dose of fifty micrograms of IV fentanyl followed by titration of small increments of IV midazolam to the desired sedation end point [(27)].

Pharmacokinetics and biotransformation

Fentanyl is rapidly distributed from plasma to highly vascular tissues (heart, lung and brain) following intravenous bolus administration. Within 5 minutes, 80% of the injected dose will leave the plasma and 98.6% by one hour. As fentanyl is highly lipophilic, it redistributes into muscle and fat and the elimination from vascular tissue occurs rapidly. The high lipid solubility and redistribution accounts for a relatively short duration of action, approximately 30 minutes when administered in increments for intravenous sedation. Fentanyl is 600 times more lipid soluble and 100 times as potent as morphine[(28)].

The majority of fentanyl metabolism occurs in the liver and intestinal mucosa via cytochrome P450 3A4 by dealkylation to norfentanyl, an inactive metabolite. Fentanyl and norfentanyl are hydroxylated and excreted in the urine. Less than 10% is excreted unchanged by the kidney and less than 10% present in faeces as metabolites.

Pharmacodynamics

Fentanyl is approximately 100 times more potent than morphine, where 0.1mg of fentanyl provides analgesia comparable to 10mg of morphine[(29)]. Peak analgesic effects occur within 1-2 minutes of IV administration and last for 30-60 minutes after a single dose, the duration of action being dose dependent. The intensity of fentanyl's effect correlates with the drug concentration at the site of action and not necessarily the plasma concentration. Serum concentrations appear to fall rapidly within 5 minutes from a peak level after IV dosage[(30)]. Nausea and vomiting are less commonly observed due to the lack of histamine release. Nasal pruritus is a commonly observed reaction with fentanyl.

Pre-assessment considerations and cautions

Hepatic and renal impairment can affect the pharmacokinetics, increasing the elimination half-life due to alterations in the clearance and plasma proteins. Similarly to benzodiazepines, the elimination half-life may be prolonged in the elderly population.

Cautious administration is required with chronic obstructive pulmonary disorder (COPD) and to patients with decreased respiratory reserve where fentanyl may reduce respiratory drive to an even greater degree than usual.

Contra-indications

Fentanyl is contraindicated in patients who have an allergy or intolerance to it. Significant liver and renal dysfunction also represent relative contraindications to fentanyl administration. Patients with renal or hepatic disease can experience more prolonged or profound effects. In these instances, lower doses and increased dosing intervals with smaller increments reduces the risk.

Drug interactions

Patients who have received monoamine oxidase inhibitors in the past 14 days should not receive fentanyl or any other opioid agonist because of the potential for severe and unpredictable potentiation of the opioid effect[31].

The efficacy of fentanyl may be reduced by inducers of cytochrome P3A4 and increased plasma concentrations with concurrent CYP3A4 inhibitors, potentially leading to mortality from respiratory suppression.

Important adverse effects:

The most frequently noted adverse effects of fentanyl are apnoea, respiratory depression, muscle rigidity and bradycardia. If these are untreated they may progress to respiratory arrest, circulatory

depression or cardiac arrest. Other adverse reactions include hypotension, dizziness, blurred vision, nausea and vomiting, laryngospasm and diaphoresis.

The respiratory-depressant effect of fentanyl lasts longer than its analgesic actions which needs to be borne in mind when discharging an apparently "recovered" patient from the dental surgery, as the escort may not be capable of recognizing respiratory depression. Fentanyl has the potential to decrease respiratory rate arising from decreased sensitivity to CO_2 stimulation, however this action is rarely observed for more than 30 minutes after drug administration. Peak respiratory depression is noted at 5 to 15 minutes after administration[32].

Respiratory compromise can potentially occur with chest wall rigidity; however this is seen with much higher doses of fentanyl than are applied in conscious sedation and has not been reported in the dental setting[33]. Fentanyl has a greater potential than other opioids for producing skeletal muscle rigidity, most notably in the muscles of respiration (thoracic and abdominal) and the vocal cords, manifesting with dyspnoea and difficulty with manual ventilation. The onset appears to be related to the rate of injection, occurring more frequently with rapid administration and prevented by the slow IV administration of the drug. The effect can be reversed by naloxone[34].

Naloxone

Naloxone is a pure opioid antagonist and reverses respiratory depression, analgesia and sedation. It is a competitive antagonist at the μ, κ, and δ receptors, indicated for the treatment of opioid toxicity associated with respiratory and/or neurological depression.

Pharmacokinetics and biotransformation

Naloxone is rapidly distributed with weak protein binding, primarily to albumin and other plasma constituents. It is capable of reaching a brain-to-serum concentration 12 to 15 times greater than morphine. The onset of action occurs within 2-3 minutes and has a duration between 45-90 minutes. It has a relatively short plasma half-life ranging from 0.5 to 2 hours. Naloxone undergoes metabolism in the liver to naloxone-3-glucuroide and is excreted in the urine.

Pharmacodynamics

Naloxone is a competitive antagonist for the opioid receptors (particularly μ receptors) and will displace an opioid from its receptor to reverse the effects, restoring an adequate level of consciousness and respiratory rate. Without the presence of exogenous opioids, naloxone will have little or no effect.

Dosing

In adults 400 μg is given initially, followed by 800 μg for up to 2 doses at one-minute intervals if there no response to the preceding dose. The dose is then increased to 2mg for one dose if there remains to be no response, at which point the diagnosis should be reviewed. If respiratory activity is further depleted then subcutaneous or intramuscular routes can be utilized for further doses, but intravenous administration has a more rapid onset of action.

Cautions

Abrupt reversal can trigger an acute sympathetic response including tachycardia, hypertension and pulmonary oedema. This concern is more significant during surgical procedures under general anaesthesia than in the dental setting where local anaesthesia is present. Caution should be exerted in patients who have developed opioid dependence (therapeutic or recreational) due to risk of precipitating opioid withdrawal. It may cause hypertension, tachycardia, ventricular fibrillation, seizures, pulmonary oedema, tachypnoea, nausea and vomiting.

Drug interactions

There are no clinically important drug interactions other than its interaction with opioids which is central to its pharmacological effect and practical use.

Important adverse effects

Reversal can be associated with nausea, vomiting and sympathetic stimulation. Persistent pain may be encountered post-operatively therefore careful titration is advised to allow for partial rather than complete reversal [33].

An opioid withdrawal reaction may be precipitated when naloxone is administered to an opioid dependent patient. The patient presents with pain (if opioid was being taken for analgesic effect), restlessness, nausea and vomiting, dilated pupils and cold, dry skin with piloerection.

1.5 Clinical monitoring for hypoxaemia

Optimising clinical monitoring is essential for conscious sedation as sedative drugs have the ability to blunt respiratory reflexes and so is crucial to the safe implementation of sedation procedures. Monitoring of the sedated patients' respiratory activity is reliant on visual assessment of the rate and depth of breathing along with pulse oximetry. Clinical observations to assess respiratory function during sedation have been shown to be unreliable with only half of the apnoeic episodes or disordered respiration identified by capnography being detected with pulse oximetry and none by visual assessment [35]. Therefore, complementary monitoring methods are desirable to improve detection of respiratory suppression. At present the routine use of capnography is not required by conscious sedation guidelines in the UK and Ireland, recommending that clinicians exert their judgment for this additional monitor based on the existing co-morbidities of the patient. Pulse oximetry will effectively measure hypoxaemia whereas hypoventilation requires monitoring of expired carbon dioxide via capnography. The lowest tolerable oxyhaemoglobin level is difficult to determine for an individual as it is also affected by cardiac output, haemoglobin concentration and oxygen demand [36].

Pulse oximeter

Pulse oximetry is a non-invasive, continuous measurement technique to detect the oxygen saturation of haemoglobin in arterial blood and the pulse rate. It consists of a microprocessor which is connected to a display where a continuous waveform is displayed to give information regarding the circulation. Alarms can be set to alert for low saturations (usually SpO_2 <90%), absence of pulse, bradycardia and tachycardia.

The basic principle of pulse oximetry relates to the differential absorption of red and near-infrared (IR) light, whereby oxyhaemoglobin (O_2Hb) absorbs greater amounts of IR light and lower amounts of red light compared to deoxyhaemoglobin (HHB). The pulse oximeter probe consists of two parts, light emitting diodes and a photo-detector. Two light-emitting diodes emit red and IR light at frequencies of 660nm and 940nm respectively, which are detected by a photo-detector on the opposing side[37]. The amount of red and IR light absorbed by the photo-detector determines the estimated amount of oxygen bound to arterial haemoglobin.

The pulse oximeter probe is usually attached to the finger as it must be placed where a pulse can be detected. Arterial and venous haemoglobin are distinguished as a result of the amount of red and IR light absorbed, which fluctuates within the cardiac cycle. During systole, the arterial blood volume increases and then decreases during diastole, whereas the blood volume in veins and other tissues remains relatively constant. The photodetector generates a voltage proportional to the light transmitted through the tissues without being absorbed[38]:

"Direct Current" (DC) – Light absorbed by non-pulsatile tissue (constant)

"Alternating current" (AC) – Light absorbed by pulsatile blood (non-constant)

The microprocessor analyses both the DC and AC at 660nm and 940nm. The absorption by O_2Hb and HHb at these two wavelengths is very different, providing good sensitivity. The amplitude of absorbances calculates the Red:IR Modulation ratio: $\boldsymbol{(R)^4}$

$$R = \frac{(A_{red,AC} / A_{red,DC})}{(A_{IR,AC} / A_{IR,DC})}$$

R is a double-ratio of the pulsatile and non-pulsatile components of red light absorption compared to IR light absorption. This ratio is determined over a series of pulses by the microprocessor to determine the SpO_2 based on a calibration curve. This calibration curve was developed empirically by measuring the ***R*** value in healthy volunteers whose saturations were adjusted to between 70-100%. As a result, any SpO_2 reading below 70% should not be considered quantitatively reliable [39].

The Beer-Lambert Law of absorbance explains how pulse oximeters are able to distinguish arterial from venous blood and tissues, measuring changes in absorbance over time:

Beer's law - The intensity of transmitted light decreases exponentially as the concentration of a substance increases.

Lambert's law - The intensity of transmitted light decreases exponentially as the distance travelled through the substance increases.

The deficiency of pulse oximetry is that a normal SpO_2 reading cannot exclude hypoventilation which occurs when respiratory mechanisms are suppressed because the alveolar-arterial oxygen difference is not measured. Arterial oxygen saturations are required to fall before pulse oximetry is able to detect the decrease in ventilation. In addition to this, supplemental oxygen delivery will further inhibit the ability of pulse oximetry to reflect the gaseous exchange at the alveolar level [(40)].

This feature influences our practice in dental sedation to withhold routine delivery of supplemental oxygen, in order to preserve the function of the pulse oximeter to indirectly detect hypoventilation. This practice has been discouraged by some authors who express concerns as hypoventilation plus hypoxaemia have a much greater potential for deleterious effects [(41)].

2. Literature review

Conscious sedation practice within dentistry has been established to become common place, particularly in the speciality of Oral Surgery where more anxiety-provoking and compliance demanding procedures are involved. There has been much research within the medical literature on procedural sedation investigating multiple end points, however the database of evidence contributing to conscious sedation in dentistry is relatively much less populated. The development of guidelines pertaining to conscious sedation has been limited on a number of grounds including lack of research specific to the dental environment, poor-quality evidence and deficiency of new evidence in the area. This was acknowledged in the foreword of the updated IACSD guidelines in 2020 " in the absence of new clinical evidence or safety issues, it was not necessary to make any substantial changes to original guidance"[6].

A review of the dental literature was performed primarily to assimilate the reported incidence of hypoxaemia with fentanyl and midazolam, inclusive of various heterogenous methodologies. The intention was to identify strengths and weaknesses in the existing evidence base to help inform our study methodology and maximize the external validity.

The primary aim is supported by additional literature framing the context and rationale for this study. A commentary on previous advanced sedation research in dentistry is provided, where a variety of sedatives techniques have been employed in an attempt to identify efficacious methods and avoid recourse to DGA. An appreciation of the attitudes and controversies between dental and anaesthetic colleagues is illustrated, which may be partly responsible for some barriers to implementing advanced techniques. A range of attitudes have been identified, with some considering these techniques to be tantamount with general anaesthetic and therefore not be performed out with the hospital environment. However, advocates support the provision in the outpatient setting, purposefully allowing patients to be managed safely and effectively. Examining the benefits of advanced techniques from both the patient and surgeon's perspective is necessary to warrant the potential for increased risk of adverse respiratory effects.

Aim

To explore the existing scientific evidence to assess the incidence of hypoxaemia associated with intravenous fentanyl and midazolam conscious sedation for patients undergoing oral surgery.

Objectives

The objectives of this literature review are to contribute to the following:

- Identify the rate of hypoxaemia with fentanyl and midazolam, assess methods of how this is measured and identify risk factors for desaturation
- Accumulate the attitudes towards advanced sedation techniques in dentistry among dental and anaesthetic professionals
- Assimilate the research on other advanced sedation techniques contributing to the dental evidence base
- Gather evidence on the benefits of advanced sedation techniques
- Identify reported complications with intravenous midazolam and fentanyl sedation
- Compare these findings in the dental literature to the medical literature

Search methods

Electronic searches of the online databases relevant to the aim and objectives of this literature review were performed in February 2020. The search strategy was employed on Medline, Web of Science and Scopus. The following "Mesh" terms were entered into the Medline search builder:

"Hypoxia", "Hypoxaemia", "Midazolam", "Fentanyl", "conscious sedation" and "procedural sedation".

Inclusion criteria

Articles selected for inclusion in this literature review required the following:

- Patients sedated with intravenous fentanyl and midazolam
- Report the incidence of hypoxaemia
- Specific to oral surgery procedures

- Adult patients
- Written in the English language
- Original research
- Relevance to this literature review

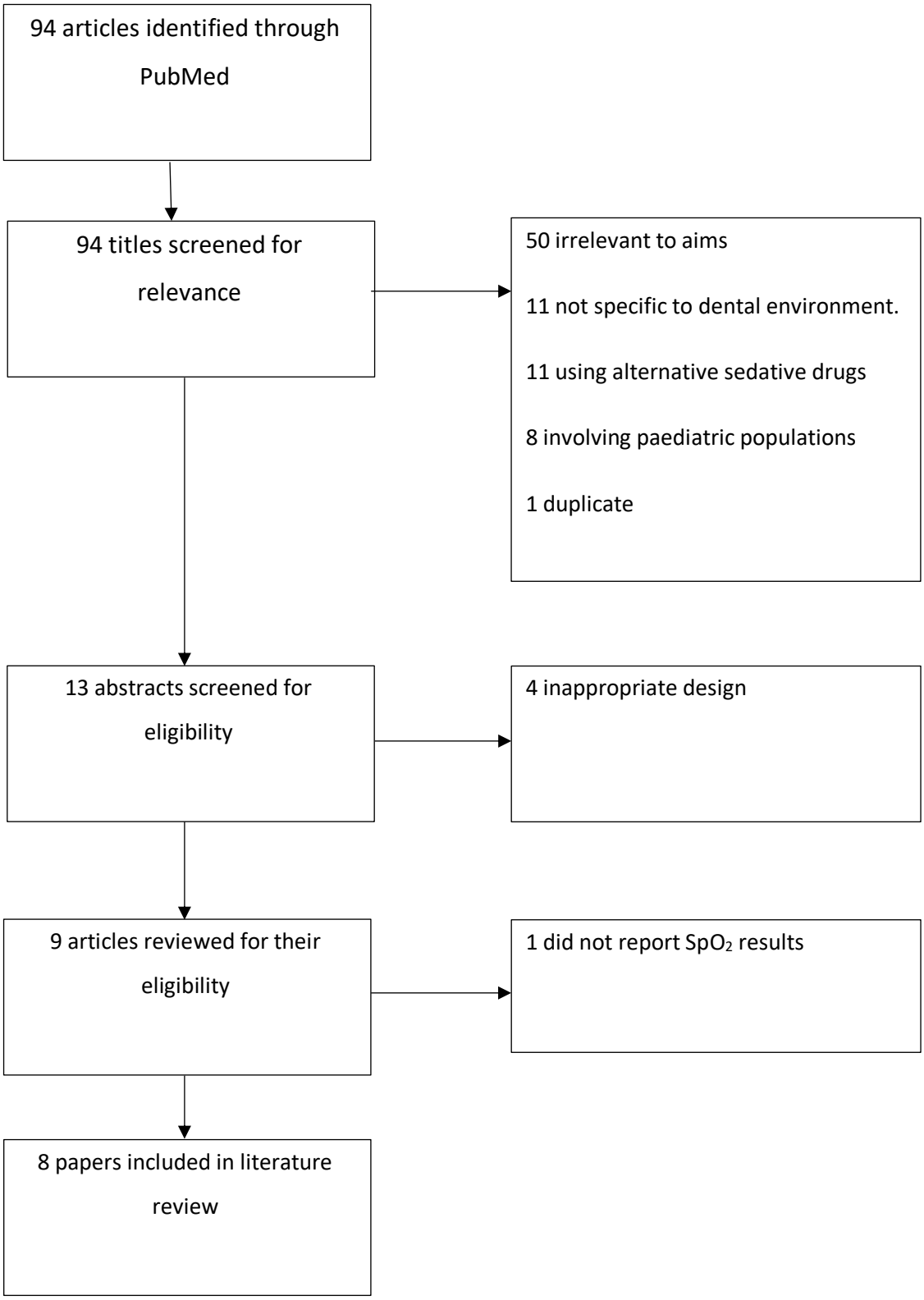


Figure 3: Search methodology for article inclusion to literature review.

Table 2: Summary of papers identifying rate of hypoxaemia with intravenous fentanyl and midazolam sedation for dental procedures.

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
The safety and efficacy of outpatient midazolam intravenous sedation for oral surgery with and without fentanyl. **Milgrom et al. 1993** **Double blind, randomised, placebo - controlled trial.** **N= 207** **Age: mean 25.7years (5.3)** **Female: 118** **Male: 89**	Null hypothesis: Combined drug therapy results in significantly poorer safety but no difference in efficacy compared to the single drug approach.	Routine delivery of supplemental oxygen at 5L/min via nasal mask.	Five groups 1. Saline (placebo) 2. Midazolam 1mg/min to clinical end-point 3. Midazolam 1mg/min to clinical end-point with additional midazolam intra-op 4. Fentanyl 1ml/min and midazolam 1mg/min 5. Fentanyl 1ml/min and midazolam 1mg/min & methohexital 10mg bolus with methohexital intra-op.	Fentanyl caused significant respiratory depression immediately during and following titration of the midazolam. 2 (3%) group 2 where apnoeic compared to 50 (63%) group 4. All apnoea was short-lived. Group 3 had twice as many subjects with $EtCO_2$ levels 25% greater than baseline, but not statistically significant between groups. No intra-operative episodes of apnoea. Group 4 required significantly less midazolam, mean 0.055mg/kg (0.025) compared to group 3, mean 0.083mg/kg (0.039) ($p<0.001$). Trained, blinded observer reported better sedation in group 4 than group 3.Subjects in group 4 did not report greater relief of anxiety or pain than group 3. At a given pain level, group 4 condition was 4.4 times more likely to produce excellent sedation versus good, fair or poor than group 3 ($p=0.004$).	Multi-centre study. Titrated sedatives to clinical end point. Same surgeon for all procedures. No difference in pre-op anxiety between groups. Apnoea clearly defined as no respiration for > 30 seconds, instigating verbal prompt.	Multiple outcomes investigated with no power calculation for sample size to detect difference. Supplemental oxygen given throughout. Doses and drugs not utilized in dental conscious sedation. Unsure why methohexital used as not included in analysis.

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
Propofol and fentanyl compared with midazolam and fentanyl during third molar surgery. **Parworth et al. 1998** **Double blind, randomized controlled trial** **N = 57** **Age: 19- 41,** **mean 25.5years(5.7)** **Female:15** **Male: 9**	Measure the safety and efficacy of propofol combined with fentanyl as sedative agents during third molar outpatient surgery.	Routine delivery of supplemental oxygen 4L/min via nasal cannula.	Fentanyl 100µg over 2 minutes, followed by random administration of either: Propofol 300µg /kg IV boluses to end point. Midazolam infusion at a rate of 75µg /kg/min until end point . Additional 25% of the initial bolus given to maintain the sedation.	No significantly significant respiratory depression was recorded. 2 subjects receiving M+F and 1 in the P+F group experienced apnoea > 20 seconds, breathing again when prompted with no need for ventilatory assistance. No statistically significant difference in average values of systolic or diastolic blood pressure, respiratory rate or SpO_2 between both groups, with both showing a significant increase in heart rate. Subjects in the M+F group were significantly more cooperative than the P+F group at both 5 and 15 intraoperative minutes (p=0.019). Amnesia was greater in the M+F group with 37.7% recall of pictures shown intra-operatively compared with 45% recall in the P+F group, but not statistically significant.	Good study design, high on hierarchy of evidence	Vital signs recorded at 15 minute intervals. 3 drop outs due to inability to tolerate surgery with the sedation, requiring GA, no intention to treat analysis. Unblinded surgeon observer for co-operation score. Supplemental O_2. randomisation technique, recovery measured to 45min.

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
Comparing efficacy and safety of four intravenous sedation regimens in dental outpatients. **Dionne et al. 2001** **Double-blind, randomised controlled trial.** **N= 997**	1. Assess relative efficacy of prototypic sedative drug regimens for dental outpatient sedation; 2. determine the incidence of common adverse drug and premorbid physiological changes predictive of serious adverse events; 3. establish standard research methodology for evaluating future therapeutic strategies for outpatient sedation.	Routine delivery of supplemental oxygen 3L/min via nasal mask or cannula.	5 groups: 1. Saline (placebo). 2. Midazolam. 3. Midazolam and intra-op midazolam. 4. Midazolam and fentanyl. 5. Midazolam, fentanyl and methohexital. Administered via: Fentanyl 50µg /ml, fixed dose administration 1.4µg /kg slow IV infusion over 2min. Midazolam 1mg/min to clinical end point (max 15mg). Midazolam titration 1mg/min followed by 10mg bolus methohexital .	Oxygen saturations were only reduced to a small extent(98%) with the addition of fentanyl as well as elevated $EtCO_2$ levels. A small number of transient apnoeic episodes were observed with midazolam alone (3-7%) and much more frequently when combined with fentanyl (48-50%). Patients in group 5 reported significantly less anxiety and pain than all other groups. Greater amnesia was reported in group 3 and 5 who received additional intra-operative sedatives. Efficacy rating by the oral surgeon differed from the patient, reporting significantly more movement during local anaesthetic administration in groups receiving midazolam. Group 4 and 5 were observed to have significantly less verbalisations of pain or discomfort.	Multi-centre study performed simultaneously at five sites. Operator blinded to sedative medications delivered.	No power calculation for sample size required to detect difference. Drugs given by anaesthetist, not operator-sedationist model. Vitals measured at 5 minute intervals. Supplemental oxygen delivered throughout.

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
A comparison of midazolam and midazolam with remifentanil for patient controlled sedation during operations on third molars. **Garip et al. 2006.** **Double blinded, Randomised controlled trial.** **N= 40** **Age: 17 – 37** **Female: 23** **Male: 17**	Compare patient satisfaction, cooperation and clinical efficacy for midazolam vs. midazolam & remifentanil for patient controlled sedation during 3rd molar surgery.	Not given routinely. 3L/min via nasal cannula if persistent desaturation below 95%.	Initial IV bolus midazolam 0.03mg/kg to all, followed by PCA: Midazolam group: 2ml 0.5mg/ml for each bolus dose Max – 12mg/hr. Midazolam - remifentanil group: 2ml 0.5mg/kg and 12.5µg /ml remi. Max - 12mg/hr midazolam & 300µg /hr remi. Lock out period 5 min.	Single drug group: No SpO_2 < 97% Multi-drug group: 10 patients desaturating < 95%. Hypoxaemia: Significant difference detected between groups at 30 minutes, SpO_2 in multi-drug group 95.9% (1.59), significantly lower than single drug group 97.4% (1.6) $p<0.05$ All reversed by verbal command, except one patient requiring triple airway manoeuvre and supplemental O_2. No significant difference between groups for total dose of midazolam, total number of requests for analgesia or the successful mean number of requests. No significant difference between systolic and diastolic blood pressure. Heart rate significantly lower in multi-drug group after 30 minutes.	Randomisation sealed concealment. Appropriate exclusion criteria Same surgeon operating in each case.	Patient Controlled anaesthesia – not practiced routinely in UK and Ireland for dental sedation. Patient was able to request bolus drug delivery until last suture placed, much longer than would be observed in our practice of sedation. Vital signs measured at 10 minute intervals, not continuous. Young cohort 17-37 years. Small sample size, no power calculation. Greater proportion of females (23) compared to males (17).

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
A comparison of the effects of midazolam/fentanyl and midazolam/tramadol for conscious sedation during third molar extraction. **Goktay et al. 2011.** **Double blind, randomised, placebo - controlled trial.** **N= 60** **No demographic data**	Evaluation of the effects of fentanyl and tramadol used in combination for sedation in 3rd molar surgery.	Not given routinely. 3L/min if persistent desaturation below 95%.	Initial IV bolus midazolam 0.3mg/kg to all, followed by: Group A: 2ml saline (placebo). Group B: 2ml IV 1µg /kg fentanyl and saline. Group C: 2ml IV 1mg/kg tramadol and saline. Additional 1ml bolus of midazolam intra-op as required.	No oxygen desaturations less than 98% observed between groups. No significant difference in heart rate or SpO_2 between groups. Mean blood pressure significantly lower in group A than group B at 40 minutes. Pain scores assessed by 'visual analogue scale' did not differ significantly post-operatively. No difference in patient and surgeon satisfaction between groups. Group B (M&F) required significantly less midazolam compared to others significantly less than other groups.	Randomisation sealed concealment. No drop-outs.	Poor definition of study outcomes. No power calculation for sample size. No data on balancing groups for baseline characteristics. No demographic detail given for age and sex proportions. No detail on how often vital signs were recorded, suggested to be 10min intervals from graphic results. IV sedation delivered by anaesthetist, bolus doses administered rather than titrating to effect. Multiple analyses – 'dredging the data' for statistically significant result.

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
Analysis of oxygen saturations recoded during dental intravenous sedations: A retrospective quality assurance of 3500 cases. **Viljoen et al. 2011** **Retrospective** **N = 3500**	Can safe oxygen saturations (≥ 94%) be consistently maintained by a single operator/sedationist? Does additional use of subanaesthetic doses of propofol increase the risk of exposure to hypoxaemia?	Routine delivery of supplemental oxygen 4L/min via nasal hood.	Firstly, slow IV midazolam to a dose of 2-5mg and titrated until sedation endpoint, followed by 50-100 µg fentanyl according to patient response. 1750 patients were sedated with midazolam and fentanyl. 1750 patients received propofol during noxious stimulation, given increments of 10-15mg. Max 33% Nitrous oxide given in most sedations.	In patients receiving fentanyl and midazolam,2.7% developed SpO_2 90-93% and 0.095% decreased to <90%. Lowest recorded SpO_2 was 86%. All patients responded to verbal commands. 4 desaturations occurred at beginning of procedure, 8 intraoperatively and the majority, 13 occurred at end of procedure when supplemental oxygen was turned off. Hypoxaemia was significantly associated with age, sex and weight. >45 years were 8 times more likely than <25 years and males 3 time more likely than females to develop hypoxaemia. The dose of midazolam, additional use of propofol or ASA grade were not significant risk factors. Results determined that a single operator/sedationist, supported by a well-trained team can consistently maintain safe oxygen levels.	Power calculation to determine 1750 patients required in each arm of the study (initial retrospective pilot study). Cases randomly selected from a data pool and all data recorded on the same standardised anaesthetic drug chart.	Retrospective data review, low on the hierarch of evidence. Reverse order of BZD and opioid delivery to our practice. No detail on how initial slow IV dose of midazolam determined. Concomitant use of nitrous oxide in most sedations. The sedationist/operator had two nursing assistants and one nurse solely for monitoring therefore not clear to what extent true sedationist/operator was observed. Data generated by only one dentist.

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
Complications associated with intravenous midazolam and fentanyl in patients undergoing minor oral surgery. **Saiso et al. 2017** **Retrospective observational** **N = 107** **Age: 9-84 (mean = 43)** **Female: 66** **Male: 41**	Evaluating the incidence, nature and sequalae of complications during and after minor oral surgery with fentanyl and midazolam sedation.	Routine delivery of supplemental oxygen at 3L/min.	Fentanyl 0.5-1µg /kg according to age. Followed by titrated midazolam 0.5-1mg/min until Ramsay sedation score 3-4. Additional doses of fentanyl and midazolam administered intra-op.	6 patients (5.6%) developed desaturation <95% after initial doses of fentanyl and midazolam, recovered with verbal stimulation. 2 patients experienced difficulty following commands, considered deep sedation. 1 patient experienced nausea and 1 prolonged recovery time. Rate of sedation related complications – 10.2%. Incidence of complications significantly higher for obese patients (P=0.008) Mean age, total midazolam and fentanyl doses, surgical duration and recovery time all greater for those who had complications.	Sedative drugs titrated to effect. Intervention for hypoxaemia defined, with verbal prompt to breathe at SpO_2 95%. Demographic data easily interpreted in tabulated form.	Validity limited by retrospective design over 12 month period. S mall sample size, single-centre. Older age group >65 than would be delivered multi-drug sedation in dental practice. Definition of complications poorly defined at outset. Supplemental oxygen given routinely. Sedation drugs delivered by anaesthetist. Vital signs recorded at 5 minute intervals. No display of vitals results. Sedation end-point farther along sedation conium than would be observed in UK & Ireland (RSS – 4).

Title, author, study design, sample size & demographics	Primary outcome	Supplemental Oxygen	Method	Results	Strengths	Weaknesses
Administration order of midazolam/fentanyl for moderate dental sedation. Lobb et al. 2018 **Retrospective observational** **N = 76** **(40 midazolam first, 36 fentanyl first)** **Age:** **Midazolam 1st : 39.33 ± 17.54** **Fentanyl 1st: 30.22 ± 15.66** **Sex: Not provided**	Investigate the effect of administration order of midazolam and fentanyl for differences in physiological parameters, drug administration times, drug dosages, patient recall and satisfaction.	Routine delivery of supplemental oxygen at 2L/min via nasal cannula.	Fentanyl first group: Fentanyl 5µg /ml administered at a rate of 1ml/min to a suitable endpoint of 25-50µg . Followed by midazolam 2minutes later 1mg/min to clinical end point. Midazolam first group: Midazolam titrated 1mg/min until clinical end point followed by fentanyl (5µg /ml solution) at 1ml/min to end point of 25-50µg .	No significant difference in physiological parameters between both groups. No significant difference in minimum SpO_2 levels, no desaturation observed below 90%. Fentanyl first group, 5 (14%) desaturated below 92%. 29% reduction in midazolam dosage when fentanyl given first is administered, 2.43mg less (p<0.001). Odds of greater patient recollection before discharge with fentanyl first, 3.13 times higher (p=0.03). No significant difference in physiological parameters between both groups Procedures started earlier with midazolam first, 4.38 min earlier P<0.001. No significant difference for recovery time (P = 0.9).	Titration of sedative drugs rather than bolus. Definition of one parameter of over-sedation given (SpO_2 ⩽90%, or requirement for an airway opening manoeuvre). Data cleaned prior to analysis. Described exclusion criteria for records lacking information for the study Despite lack of statistical significance, clinically significant desaturation reported with fentanyl first group.	Retrospective review of charts spanning a 9 month period. Single-centre. No control. Multiple outcomes assessed with no power calculation. Ambiguous and conflicting definition of end point – related to achieving dose of 25-50µg fentanyl, whereas midazolam endpoint defined by clinical signs. Vital signs measured at 5 minute intervals. Dose of fentanyl suggested by surgical procedure. No detail on who performed data cleaning.

2.1 The Sedation continuum

The sedation continuum is achieved in a dose-response manner, varying from patient to patient and is not a static point. The definition of conscious sedation equates to the moderate range of this continuum, a drug-induced depression of consciousness whereby patients retain the ability to purposefully respond to verbal commands, either alone or accompanied by light tactile stimulation. There should be no intervention required to maintain an airway, and normal mechanisms of adequate spontaneous ventilation and cardiovascular function are maintained [(42)].

The depth of sedation is primarily a clinically observed rating for which the corresponding cardiopulmonary signs do not directly translate. Therefore, this measure is vulnerable to subjectivity of the observer in assessing a patient's response to verbal and tactile stimulation. Without a tool for objectively assessing depth of sedation, the observer's interpretation of the patient's responses will remain the defining measure of the level of their sensorium on the sedation continuum [(43)].

The combination of opioids and benzodiazepines can be encompassed under the definition of conscious sedation providing that adequate safety margins are maintained. Any procedure which moves beyond the continuum into the realms of deep sedation is considered to require the same level of care as general anaesthetic and is therefore not permitted in the primary care environment. General anaesthesia is a state of unconsciousness and amnesia, complete analgesia and immobilization achieved through interaction of drugs within the CNS [(44)]. The American Society of Anaesthesiologists recommends that sedationists are trained in provision of rescue procedures proportional with one level of sedation higher that the intended end point. This would include management of a patient with bag-valve-mask ventilation and laryngeal mask airway placement.

2.2 Incidence of hypoxaemia with fentanyl and midazolam

The guidelines produced by IACSD and SDCEP recommend clinical observation and pulse oximetry for monitoring the sedated patient's respiratory effort. Supplemental oxygen can disguise the occurrence of hypoxaemia by artificially increasing arterial oxygen saturations and potentially reduce the sensitivity of pulse oximetry monitoring [(40)]. Judicious use of supplemental oxygen enables the pulse oximeter to maintain greater precision as a surrogate measure for detecting hypoventilation. Providing supplemental oxygen to the normoxaemic patient has been reported to offer minimal advantage but can detrimentally delay the operator-sedationist in detecting respiratory depression[(45)]. There has been much discussion within the literature between various specialties regarding the use of capnography for monitoring respiration. Brady et al. [(46)] were unable to provide evidence to support a change to the existing dental guidelines regarding capnography monitoring to prevent hypoxaemia in the oral surgery outpatient environment when supplemental oxygen is not routinely administered for single drug midazolam sedation.

Greater external validation for conscious sedation in dentistry is gained from research methods where supplemental oxygen is not routinely administered. Only two papers were identified in the literature search aligning with this study protocol. Garip [(47)] and Goktay [(48)] only administered supplemental oxygen at 3L/min via nasal cannula to patients with persistent desaturations beneath 95% during intravenous sedation for surgical extraction of impacted third molars. Garip compared single drug midazolam sedation with multi-drug midazolam and remifentanil in forty patients. Desaturations below 95% were noted in ten patients, equating to 50% of the multi-drug sedation group with no saturations below 97% in the midazolam alone group. The majority of hypoxic episodes were reversed with verbal stimulation, except for one patient who required a triple airway manoeuvre and supplemental oxygen. The difference in oxygen saturations between the two groups did not reach statistical significance until the thirty-minute point, when the multi-drug group's oxygen saturation levels were significantly lower than in the single drug group.

In Gotkay's double-blind, randomised, placebo-controlled study involving sixty subjects, none experienced saturations below 98%, with no significant difference in SpO_2 between groups receiving midazolam, midazolam and fentanyl and midazolam and tramadol. Haemodynamic measures

remained stable, only the midazolam group displayed a significantly lower mean blood pressure than the group combined with fentanyl. The average midazolam dose received in combination with fentanyl was lower Gotkay's study (3.99mg ± 0.89), compared to Garip's group (6mg ±2mg) who received midazolam in combination with remifentanil. Remifentanil undergoes rapid metabolic degradation and is an ultra-short acting opioid, rapidly achieving a steady-state concentration in the plasma and site of action [49].

Saiso et al.[50] administered doses of fentanyl (mean 66.8 ± 26.3µg) followed by midazolam (mean 2.4mg ± 1.7mg) and supplemental oxygen at 3L/min in one hundred and seven patients. The threshold for verbal stimulation was set at SpO_2 of 95%, at which point patients were encouraged to take a deep breath. No detail is given regarding whether or not there was a dedicated observer to identify threshold saturations. They observed SpO_2 <95% in six patients (5.6%) after initial administration of midazolam and fentanyl which were all successfully managed by verbal stimulation to take a deep breath.

Lobb et al. [51] primarily investigated the order of administration of fentanyl and midazolam and monitoring measurements were recorded at 5 minute intervals. No statistical difference was found in the minimum SpO_2 levels experienced by both groups, with the fentanyl first group experiencing five cases (14%) dropping between 90-92% and zero hypoxaemic events in the midazolam first group. The sedated patient was monitored clinically by a dedicated sedation assistant not involved in the surgery, but the study does not provide a definition for hypoxaemia or the threshold for stimulating the patient to breath once desaturation was observed.

A significant difference in respiratory depression was observed by Milgrom et al. [52] between two groups in a placebo-controlled, double-blind clinical trial undergoing mandibular third molar removal. Of the 78 patients receiving midazolam only, 2 developed apnoea (3%) compared to 50 of the 79 (63%) patients given intravenous fentanyl and midazolam. It was noted that all of the apnoea occurred after delivery of the second drug, midazolam and was short lived. Despite the high incidence of apnoea, when oxygen saturations were assessed, only 2 patients developed hypoxaemic events below SpO_2 90% in the fentanyl and midazolam group. It is not specifically clear from the methodology whether oxygen saturations were measured continuously or at intervals.

Dionne et al.[53] investigated the safety and efficacy of four different IV sedation regimes in dental outpatients undergoing third molar surgery. Sedation was performed by a research investigator in absence of the operating oral surgeon, as the surgeon was involved in subjectively assessing the patient response. Oxygen saturations and end tidal carbon dioxide were measured continuously and the research investigator noted any desaturation below 92%. However no information is given regarding if and when the patient was stimulated to take a deep breath to correct any desaturation. In the presence of 3L/min of oxygen, no desaturations occurred with midazolam alone, but the addition of fentanyl was accompanied with a small decrease in pulse oximetry to 98%. This was also associated with an elevated concentration of end tidal carbon dioxide in the group of patients receiving fentanyl. Apnoea was defined by the authors as thirty seconds without a breath and was observed in a greater proportion of patients receiving midazolam and fentanyl (48—50%) compared to midazolam alone (3-7%). The authors also noted that when the drugs are administered slowly with careful patient monitoring, these adverse events are transient and can be avoided.

Viljoen [54] retrospectively reviewed the records of 1750 patients sedated with fentanyl and midazolam, defining hypoxaemia at SpO_2<94% and an adverse event as two or more desaturations <94% during the same sedation. Supplemental oxygen was delivered at 4L/min and a total of 17,785 oxygen readings were included in the data analysis. Overall there were 497 desaturations <94% (2.795%) in patients who had received fentanyl and midazolam. The lowest recorded reading was 86%, but it is unclear if this was in the group given additional propofol or not. The majority of all desaturations less than 90% were identified to occur at the end of procedure affecting 13 patients in recovery when no supplemental oxygen was being administrated. A smaller number involving 4 patients developed desaturations at the beginning of procedure, thought to be attributed to the sedative drugs alone and recovered with verbal stimulation. Intraoperatively, desaturations were observed via pulse oximeter in 8 patients, postulated to be a result of competing factors in the shared airway.

A study by Parworth et al.[55] was designed with the aim of measuring the safety and efficacy of propofol combined with fentanyl for third molar surgery. Patients were randomly assigned to groups receiving either midazolam and fentanyl or propofol and fentanyl. A standard dose of 100µg fentanyl

was given to each group, followed by titration of the sedative drug to the patient response and vital signs. Oxygen saturations were monitored with pulse oximetry and measured at 5-minute intervals. The results based on only 33 patients in the combined opioid group found no significant respiratory depressions and all oxygen saturations recorded at 5 minute intervals were above 99%. Two participants receiving fentanyl and midazolam developed apnoea for more than 20 seconds.

Risk factors for desaturation

Pre-assessment is the cornerstone of safe practice for conscious sedition in the outpatient department. There is limited good quality evidence on risk factors associated with respiratory depression with only two papers in the literature review including this outcome in their secondary outcomes. The retrospective analysis of 3500 IV dental sedation cases by Viljoen[54] describes the variables age, sex and weight to be significantly associated with low saturations. Multiple logistic regression analysis found that males were three times more likely than females to develop low oxygen saturations and the chance of these events increased with patients over the age of 45, who were nearly eight times more likely to develop a hypoxaemic episode. The high weight group (>68 kg female, >85kg male) were twice as likely as the low weight group (<60kg female, <74kg male) to experience low arterial oxygen saturations. Little difference was found in the onset of hypoxaemia when ASA I patients were compared to ASA II. The incidence of sedation related complications was significantly higher in obese patients than in non-obese ($p<0.05$), with desaturation to 95% demonstrated in three obese patients[50]. In comparison to Viljoen, Saiso et al.[50] did not find a relationship between sedation related complications and age or sex.

2.3 Measuring sedation outcomes

Existing research has focused on investigating surrogate measures as potential for predicting patient harm, rather than measuring the occurrence of rarely reported adverse outcomes. Fleming et al. [56] describes a surrogate endpoint as "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that directly measures how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint".

The most commonly reported surrogate measures in the sedation literature are hypoxaemia, apnoea, hypotension and bradycardia which are all readily derived from standard monitoring of vital signs. The principle underlying the value of monitoring these measurements is derived from the pathophysiology of potential patient harm from sedative drugs, most likely to arise from respiratory depression leading to hypoxaemia and cardiovascular instability. The heterogeneity of definitions for these outcomes between researchers has placed limitations on the ability to develop recommendations from previous research. In the existing evidence base, there is heterogeneity with the environments and teams involved in delivery of sedation, types and doses of sedative and analgesic drugs, definition of outcomes and variability of techniques.

The "International Committee for the Advancement of Procedural Sedation" (ICAPS) was founded in 2014 with the aim to "provide an independent, international, multidisciplinary forum to facilitate open dialogue and consensus generation between experts in the area of sedation". The group has advocated use of a standardized tool with the intention to promote consistency of data collection for procedural sedation research[57]. The rarity of adverse events is discussed by the authors who highlight the need to focus attention on the more frequent events and interventions as a prelude to risks such as apnoea or instigation of rescue procedures. Intervention based definitions may better predict clinical importance rather than defining a threshold for an event, which would be immaterial if not prompting an intervention. The ICAPS committee concluded that there would be better international acceptance of this tool by omitting "arbitrary, controversial and irreconcilable" parameters which have had fluctuating thresholds and time benchmarks. The relative importance of clinical interventions and outcomes are colour coded into three tiers categorized as minor, intermediate and

sentinel. If we consider the use of this tool specific to conscious sedation in dentistry, the most likely ceiling of intervention would be the minor (green) tier i.e. addition of supplemental oxygen and least likely to reach the intermediate (yellow) tier where reversal agents are placed. This tool may be worth considering for conscious sedation research going forward to align dental contributions to the developing body of evidence using consistent definitions and generating results which can contribute to systematic and meta-analyses, thus far hindered due to the heterogeneity of existing research.

The numerical threshold at which an operator-sedationist will intervene to correct a patient displaying hypoxaemia is variable. Some authors have displayed less tolerance for desaturating values on pulse oximeter by setting threshold definitions at SpO_2<95% [47, 48, 50] versus others at SpO_2 <90%[58]. The variability of these parameters creates confusion and limits the determination of clinical significance. The clinical importance of these measures does not correlate with numerical thresholds and durations. To reduce reporting disparities and promote consistency of data collection, standardisation is required.

Viljoen is one of the few dental researchers to primarily study oxygen saturation levels during conscious sedation, identifying this measure as the greatest risk of morbidity and mortality[54]. Safe arterial oxygen saturation was defined at 94%, owing to the rationale of the sigmoidal shape of the oxyhaemoglobin desaturation curve. Once SpO_2 has reduced to 92%, desaturation may rapidly occur in patients who are experiencing apnoea or airway obstruction. Combined with the pulse oximetry margin of error of 2%[59], a threshold of SpO_2 at 94% was deemed to be a minimum safe limit. This rationale was extended to a randomised controlled trial by Brady et al. [46] investigating if the use of capnography could decrease the incidence of hypoxaemia, where a threshold of $SpO_2 \leqslant 94\%$ was defined as a hypoxaemic episode. The intervention performed at this threshold involved verbal stimulation instructing the patient to breathe. A severity scale was utilised by both of these researchers to categorize the severity of hypoxaemia as being mild ($SpO_2 \leqslant 94\%$), moderate ($90\% \leqslant SpO_2 \leqslant 92\%$) or severe ($SpO_2$<90%) [46].

Pulse oximetry is a surrogate measure for respiration, measuring arterial blood oxygenation saturation rather than alveolar ventilation[41]. Arterial oxygen saturation is measured on the premise of potential for harm which may evolve based on low arterial blood oxygen saturation. This has been extended to

multiple measurable outcomes including desaturation, hypoxaemia and apnoea with heterogeneity of definitions between researchers, limiting generalisability of the literature. Desaturation is typically defined as arterial oxygen saturation less than 95% indicating that red blood cells are not carrying oxygen at maximum capacity. Hypoxaemia is generally reported as a binary outcome, being either present or absent which has limited usefulness in further applications, such as quantifying risk of oxygen desaturation.

Niklewski et al.[60] introduced a new surrogate end point described as the "area under the cure of oxygen desaturation" (AUC_{DESAT}) to assess its relationship to anaesthetist's perception of risk. The AUC_{DESAT} provides a more sophisticated approach to monitoring blood oxygen levels during procedural sedation by giving information on the depth, duration and rate of episodes of oxygen desaturation. Overall the most important factor ranked by anaesthetists in determining patient risk for potential adverse clinical outcomes was arterial blood oxygen level, with respiratory rate being the second most important factor. Based on the data, AUC_{DESAT} scores identified groups of patients as being at low, medium or high perceived risk of complications during sedation. The AUC_{DESAT} may be more informative and clinically applicable for describing the characteristics of desaturation. This may be usefully extrapolated to determining a patient's risk for sedation, "AUC_{DESAT} given it is a single numerical variable, is an ideal endpoint for assessment of risk of adverse clinical outcomes in sedation studies". Using AUC_{DESAT} as a surrogate end point, the perception of risk can be more accurately defined through the incorporation of incidence, depth and duration of oxygen desaturation.

Sequence of opioid and benzodiazepine administration

The recommended technique for administration of multi-drug sedation involves fentanyl first followed by midazolam [12]. The conscious sedation protocol in Cork Dental Hospital was derived with anaesthetic colleagues, to consist of an initial loading dose of 50μg of fentanyl followed by titrated midazolam, at a rate of no greater than one milligram per minute to the sedation end point. There is a small body of evidence in the literature supporting the potential for reduction in benzodiazepine dose required to achieve sedation end point when preceded by fentanyl. Research by Moore et al.[61] supports the delivery of opioids first allowing for a substantial reduction in the total dose of midazolam titrated to effect, demonstrating a 36% reduction in the amount of midazolam required when fentanyl was administered first. Lobb et al.[51] found an average reduction of 2.43mg in midazolam dose when

fentanyl was administered first. This demonstrates the importance of considering the pharmacodynamic interaction between fentanyl and midazolam for conscious sedation, where the effects are synergist and not additive [3].

Other authors have advised that the order of sedative drug administration should be determined at the discretion of the sedationist, or based on assessment of the individual patient needs [62]. Weaver suggested that a sedative first approach should be adopted when the patient's needs are primarily due to anxiety or desire for reduced recall. If management of pain is the expectation, then an opioid first approach was to be considered a better option. There is very poor-quality evidence to support this claim. Khader et al. [63] investigated the effects of the two different sedation sequences on patient's pain perception and vital signs via a prospective randomised controlled trial. They found that there was no significant difference between vital signs from baseline to the end of surgery in each group. Patient pain scores were measured using Wong-Baker FACES pain scale, which also failed to find significant difference in the pain scores at 24 hours between the two groups. Nevertheless, the authors concluded that the administration order should be tailored to the patient's needs, type of surgical procedure and surgeon preference. The weight of existing evidence appears to support the delivery of a pre-determined dose of opioid with the level of sedation gradually increased with small incremental doses of the benzodiazepine until the optimal level of sedation is achieved.

Achieving sedation end-point with Fentanyl and Midazolam

Sedative drugs are titrated to a clinically determined end-point for intravenous sedation. Use of fixed doses or bolus techniques are unacceptable. In order to maintain the wide margin of safety, titratable techniques must be adhered to . The patient is monitored for features of a relaxed patient with sufficient anxiolysis to allow treatment to proceed. Signs typically include slowing and slurring of the speech, partial ptosis and reduced motor coordination, with the patient retaining ability to obey instruction and maintain verbal communication [19, 64].

The Ramsay Sedation Scale (RSS) consists of six levels to categorise the level of sedation a patient has achieved; the first three categories describe an awake patient and three asleep. This scale was first described in 1974 for patients who had been given alphaxalone - alphadolone in an intensive care

unit. Its use has been criticised due to the inherent subjectivity and poor validity, however some report the good reliability, inter-observer agreement and consider it to be a reproducible tool for clinical monitoring of the sedated patient [65].

The most commonly used score to quantify the intra-operative level of sedation used in the literature is the RSS [47, 50]. Previous research methodology has aimed for range of RSS scores (Table 3), varying from Ramsay 2 [48] to Ramsay 3-4 [50, 51]. For dental outpatients, we advocate maintaining a sedation score between 2 to 3 in the oral surgery department, helping to maintain intra- and inter- patient consistency of sedation level achieved. Aiming for RSS score of 4 or greater is beyond the accepted definition of conscious sedation as these describe patients who are asleep.

Table 3: Ramsay Sedation Scale

Level	Characteristics
1	Patient awake, anxious, agitated, or restless
2	Patient awake, cooperative, orientated and tranquil
3	Patient drowsy, with response to commands
4	Patient asleep, brisk response to glabella tap or loud auditory stimulus
5	Patient asleep, sluggish response to stimulus
6	Patient has no response to firm nail-bed pressure or other noxious stimuli

2.4 Attitudes to advanced sedation techniques in primary dental care

The IACSD states that “patients have the right to expect a high-quality service to meet their dental needs”. Whilst it is accepted that patients should be managed with the least intervention effective to facilitate their treatment, judicious use of the advanced sedation techniques may improve access to dental services, avoiding recourse to DGA which can increase waiting times, healthcare costs and create health access inequalities in certain regions of the country. Treatment planning for dental patients under general anaesthetic may favour more finite options than would otherwise be considered under sedation, such as extracting potentially restorable teeth in order to reduce the likelihood of repeating DGA.

Guidelines advise that alternatives to DGA should be explored in the first instance for other appropriate options. The void between treatment under local anaesthetic and general anaesthetic has been successfully filled by conscious sedation. Albeit there is a limited evidence base, the failure of reported adverse events has served to support the contribution of this modality to the behavioural management armamentarium. The distinction between standard and advanced techniques are outlined in the SDCEP guidelines which recommends that if sedation is considered necessary for the delivery of dental care, preference should be given to the standard techniques, unless there are clear indications to do otherwise. Advanced techniques are to be considered only when the clinical needs of the patient are not suited to using a standard technique.

Advanced techniques employ a variety of sedative and analgesic drugs including opioids, propofol, ketamine and sevoflurane, the combinations of which can be less predictable than singe drug techniques. As a result, caution is to be exercised with the use of these drugs due to the narrower therapeutic indices which may increase the capacity for adverse events. The use of advanced techniques has significant considerations for dental team training, staffing and equipment to meet the requirements which exceed those in the standard techniques. Such measures have been outlined by the IACSD report which states the sedation team must have immediate access to the equivalent range of skills and facilities to be found in an acute trust for the prompt recognition and immediate management of adverse events.

Dental attitude to advanced sedation techniques

Treatment planning decisions must indicate the justification for escalating to advanced techniques which may be in relation to medical, dental, physiological or sedation-related requirements. Robb [(66)] presents a case series of patients who were ineffectively managed with standard techniques for reasons including inability to achieve anxiolysis, limited co-operation or tolerance to benzodiazepines. Anecdotal evidence is discussed, where the experienced sedationist is able to recognise the subjective features of an adequately sedated patient with midazolam yet the patient still verbally describes or physically reacts anxiously during treatment.

The over prescription of DGA has been recognised as a potential burden on limited health care resources and has implications for patient safety. The attitudes of Oral and Maxillofacial Surgeons in the UK for adult dental extractions under DGA was assessed via an electronic survey in 2016[(67)]. The survey identified a culture of demand-driven adult DGA mainly by the 'consumer' and considered to be a recent luxury. This culture needs to be addressed owing to the risks associated with anaesthetics and the impact on health service resources. The greatest driver for DGA demand was perceived to be dental anxiety (28%), a primary indication for conscious sedation. However 27 of the OMFS units responding to this UK based survey did not provide sedation services and where sedation was provided, this was mostly anaesthetic led. This survey indicated that there is a strong perception of patients feeling entitled to an "a la carte service", potentiated by lack of sedation provision in some units. The problem is further compounded by clinicians' decisions on patient care potentially being influenced by governance factors such as patient complaints.

Whilst advanced techniques have gained acceptance for adult patients with the operator-sedationist model, the provision of this service for children remains under the remit of our anaesthetic colleagues. A survey of 1,219 Canadian paediatric dentists recorded their attitudes to conscious sedation, of which 743 (63%) were actively practicing sedation[(68)]. The main deterrent in providing this service was a fear of liability, whereas factors influencing increased willingness to deliver sedation services related to experience, training and remuneration such as experience administering sedation more than three days per week, rating their sedation training as "good or excellent" and had 11% or more patients with public insurance.

Anaesthetic attitude to advanced sedation techniques

A survey of 253 anaesthesiologists attitudes (64% response rate) to the provision of sedation services by dental practitioners in primary care was completed by Consultant Anaesthetists in Scotland in 2004[69], pre-dating the pivotal IACSD guidelines by over ten years. This survey was performed on foot of the UK Department of Health document "A conscious decision" which invoked the change for general anaesthetics for the provision of dental treatment to be permitted only in a hospital setting with consultant anaesthetists. Whilst only 12% were actually involved in delivery of DGA services for dental procedures, the opinions of the anaesthetists were quite variable. A majority disagreed with the dentist acting in an operator-sedationist capacity and 71% disagreed with dentists using midazolam and fentanyl in hospital practice. Furthermore, a very large proportion (90%) disagreed with use of these sedatives in dental practice. There were a concerning number of anaesthetists who felt it was inappropriate for dentists to even provide standard sedation procedures, but recognised that the provision of all dental sedation services was unrealistic for the anaesthetic profession. There was agreement (59%) that dentists should receive training to practice conscious sedation. With the publication of the detailed content of syllabus by the IASCD, it would be interesting to see if these attitudes have now changed.

This attitude was closely mirrored by anaesthetists in 2010 working in central western Brazil where 111 anaesthetists responded with 92.8% disagreeing with the provision of moderate sedation by dentists in primary care[70]. Only 5.4% of respondents were routinely practising DGA and these anaesthetists were among the most resistant to dentists performing moderate sedation. The authors describe the level of education and training for dental conscious sedation in this jurisdiction, dictated by the Brazilian Dental Association, with a legal requirement for ninety-six hours of training to educate practitioners on inhalation sedation with nitrous oxide and oxygen. The reason provided by many anaesthetists voicing their disapproval of dental sedation procedures was related to a perceived lack of confidence in competency and inadequate training of the dental team.

2.5 Evidence for advanced sedation techniques in dentistry

The lack of high-quality evidence in the field of conscious sedation in dentistry is particularly limiting for advocating advanced sedation techniques which are far less widely practised than standard single drug sedation. Whilst the definition of conscious sedation describes the state which should be achieved, it does not prescribe how to achieve it. There are various techniques and drugs which may be employed to achieve conscious sedation, providing that the adequate margin of safety is maintained. The evidence for advanced sedation techniques reported in the literature over the past twenty years have stimulated plenty of debate. Two particular papers[71, 72] stimulated a stream of correspondence within the 'Anaesthesia' journal which shed important light on the controversial aspects regarding the application and commissioning for advanced sedation techniques in dental services.

Although nitrous oxide is a well-established technique with an excellent safety record, failure leads to escalation of pharmacological behavioural management to either intravenous conscious sedation or general anaesthesia. Lahoud and Averley[73] sought to determine the safety and efficacy of an acceptable alternative to avoid recourse to DGA, particularly when nitrous oxide inhalation sedation had failed and the use of intravenous sedation would carry an unacceptable risk. Following a successful pilot study[74] involving 75 healthy children (3-15 years), Lahoud and Averley performed a randomised controlled trial comparing a mixture of sevoflurane and nitrous oxide mixture with nitrous oxide alone for children undergoing inhalation sedation for dental treatment. The children included in the study were between 3-10 years and a significant difference in the successful completion of dental treatment was observed between the two groups. Sevoflurane was administered in low concentrations between 0.1-0.3% to supplement nitrous oxide and oxygen which facilitated successful completion of dental treatment in 89% (215/241) of children compared to 52% (89/170) who received nitrous oxide alone. The lowest observed arterial oxygen saturation was greater than SpO_2 97% in 96% of children given nitrous oxide and 97% of children given sevoflurane with no significant difference in oxygen saturations between the groups during treatment or recovery. The technique involved 60% inspired oxygen concentration therefore carried a negligible risk of desaturating below 95%.

From the results of the study, the authors concluded that for every 100 children administered sevoflurane/nitrous oxide, 37 children would avoid recourse to general anaesthetic compared to nitrous oxide alone. In the absence of any adverse effects, this technique was postulated to be "safe, practical and significantly more effective than nitrous oxide alone in children having dental treatment." The simple practical technique is recommended by the authors for use by trained anaesthetists being both cost effective and having wide clinical applications.

To continue the endeavour to find suitable alternatives to DGA, Averley et al. [71] published another single centre randomised control trial in 2004, performed in a large primary care centre in the North East of England. The aim was to assess if combining the use of intravenous midazolam with nitrous oxide or nitrous oxide/sevoflurane would be more likely to result in successful completion of dental treatment than midazolam alone. Secondly the study sought to determine if this technique was admissible as an alternative to DGA. Sedation was delivered by anaesthetics and recruited a total of 697 children whose anxiety levels precluded inhalation sedation. The participants were randomly assigned to three groups:

- Group 1 – inhaled medical air and titrated IV midazolam.
- Group 2 – combination of inhaled 40% nitrous oxide in oxygen and titrated IV midazolam.
- Group 3 - combination of inhaled mixture of sevoflurane 0.3% and nitrous oxide 40% in oxygen with titrated IV midazolam.

A significant difference was observed between the groups regarding the number of successfully treated children in each group: group 1, 54% (94/174), group 2, 80% (204/256) and group 3, 93% (249/267). The most effective technique from this study was observed to be the combination of intravenous midazolam and inhaled sevoflurane with nitrous oxide/oxygen. All children remained responsive to verbal commands and no significant adverse effects were observed during the study. Minor adverse events included six cases with vomiting of clear fluids which occurred in group 3. Despite the low prevalence of vomiting being just over 2%, fasting protocols were recommended as a precaution when more than one agent is administered. Other benefits outlined by the authors included improved compliance for cannulation and reduced doses of midazolam with good amnesia. At the time of writing the paper, development of guidelines on paediatric sedation remained in progress. A point of potential contention was acknowledged in the discussion, that these "effective

and apparently safe" conscious sedation procedures where performed in specialist, primary care centres with the support of anaesthetics and appropriately trained and experienced teams. This study heralded the emergence of evidence to support intravenous sedation in combination with inhaled agents for dental procedures. This contributed to an evolving area of interest, creating an evidence base of potentially suitable alternatives to DGA providing proper care and attention could be exercised outside the hospital environment.

This article roused a response from Lahoud[75], asserting his viewpoint by reminding the reader of the events leading to "A Conscious decision" in 2000, following the report of five mortalities arising from general anaesthetic in dental practice between 1996-1998, instigating the cessation of general anaesthesia in dental practice. He based his arguments on two grounds, firstly questioning why the authors had taken unnecessary risk by combining intravenous midazolam to the mixture of sevoflurane and nitrous oxide, when his previous pilot and randomised controlled study with Averley found the combination of inhalation agents to be safe and effective for paediatric conscious sedation. Further to this, the technique had been safely applied to hundreds of patients inclusive of both the practice and hospital settings. Modification of the technique with the addition of intravenous midazolam potentially narrowed the safety margins, risking encroachment upon deep sedation or general anaesthetic. Secondly, to promote these techniques in the primary care setting would fly in the face of danger and urged the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland to prohibit the use of intravenous sedative in children under the age of 16 outside of the hospital environment for dental treatment.

In his reply, Averley agreed with Lahoud that poorly controlled sedation could risk deep sedation, emphasising that this risk was reduced through the pre-requisite of an appropriately trained sedation team including the anaesthetist and dentist. He defends their research confirming how they carefully selected patients for advanced techniques which were only administered to children whose only alternative would have been DGA. Averley strongly contests Lahoud's remarks, reserving advanced sedation techniques solely for children in the hospital setting, re-iterating that the training of the staff involved in delivery of sedation would be more critical: "the issue is expertise, facilities and service organisation, not location". Considering the longitudinal landscape for advanced sedation procedures, Averley felt that the dental surgery was more suitable to meet all the dental needs than an operating theatre, therefore avoiding repeated cycles of failed dental treatments under general anaesthesia.

Research on advanced sedation techniques has also extended to patient-controlled sedation where Leitch et al. conducted a partially blinded randomised controlled trial of patient-maintained propofol sedation and operator controlled midazolam sedation in third molar extractions[72]. A greater mean reduction in anxiety (p=0.010) was recorded with the visual analogue scale for patients receiving propofol (21mm) compared to those who received midazolam (11mm). The propofol group displayed a significantly higher minimum arterial oxygen saturation (97.8%) compared to the midazolam group (97%). Only one patient desaturated to 88% which was observed in the operator delivered midazolam group, none of the propofol patients experienced oxygen saturations less than 93%. The recovery nurses were blinded to the sedative technique and found the propofol group to recover on average 7 minutes faster than the midazolam group. No significant adverse events were noted with both techniques, with propofol preforming superiorly with regards to improved anxiolysis, shorter recovery time, less depression of psychomotor function however comparably these patients experienced less amnesia than the midazolam group.

The published research from Averley et al. and Leitch et al. prompted a letter from Wildsmith[76] who acknowledged the need for advanced techniques but referred to the methodology of each study where sedation was led by a consultant anaesthetist, contesting the applicability of such techniques to the operator-sedationist in general dental practice. Further to this, the dental team in Leitch's study also employed an anaesthetic assistant and recovery nurse which would be difficult to remunerate in primary care. Wildsmith questioned what non-human resources would be required for these techniques and whether the authors felt their techniques should be appropriated to the hospital or similar setting?

In response, Averley made no attempt to justify the use of the combined inhalation and intravenous drugs by the single-handed operator sedationist. Their overarching intention was to support the evidence base for safe, patient-centred and cost -effective techniques which were aligned with the General Dental Council's definition of conscious sedation with procurement of anaesthetic led sedation key to fine control of safe levels of sedation. The sedative techniques described did not warrant any additional non-human resources compared to general anaesthesia but stated that the application should be reserved for specialist primary care centres where appropriately trained expert teams could be assembled.

To address the same letter from Wildsmith, Leitch outlined the reason compelling their interest in investigating propofol, owing to a lack of assurance over the complete safety of incremental intravenous midazolam and cited endoscopy procedural sedation literature. He supported his rationale by explaining the pharmacokinetics, whereby 60 second intervals between midazolam doses may not be sufficient to allow equilibration between the blood and effect site. As their paper had demonstrated, the greater safety of patient-controlled sedation could contribute towards another technique to challenge the current dogma, but not advocating use in general practice until further research could support the technique.

Finally, Greenhalgh[77] weighed in on the debate contributing a very relevant point that had so far been overlooked between these correspondences. The characteristics of the dental phobic patient have a tendency towards those who may already be taking prescribed anxiolytics resulting in a tolerance of conventional midazolam doses, coupled with a lower pain threshold which may preclude effective standard techniques. If we consider the source of anxiety and fear, these are often reported to relate to local anaesthetic injections and the potential that one might experience discomfort during the procedure. Patient expectations of sedation are often distorted as the concepts of analgesia and anaesthesia can be difficult for the lay man to differentiate. A large portion of patient need is unmet by neglecting to consider analgesic concerns which cannot be attended by local anaesthetic alone, such as the forceful pressure associated with dental extractions. Therefore combining sedative with a short acting opioid may be more effective in achieving the outcomes that anxious patients desire.

To conclude the debate in 2005, Wildsmith remained very concerned that Averley had persisted in advocating for the combination of midazolam, sevoflurane and nitrous oxide in specialist primary centres. The difficulty with this would be guaranteeing consistent high standards among other practitioners if this practice where to be permitted in primary care. The irrelevance of Leitch's argument drawing parallels on the safety of single drug midazolam in dentistry to endoscopy was highlighted, as the majority of adverse events occurring in endoscopic sedative procedures were attributed to polypharmacy and significantly the inability to administer local analgesia for pain control, requiring more systemic analgesia. Wildsmith focuses on the point that further research should be dedicated to sedative techniques which are suitable for deployment in primary care where the majority of dentally anxious patients will be managed.

Anaesthetic colleagues have pursued investigations for utilization of propofol for ambulatory dental procedures owing to its short duration of action and short half-life. Burns et al. [78] performed a double blind, randomised controlled trial comparing a target-controlled infusion (TCI) of propofol with patient-controlled (PCS) propofol for sedation in combination with a small concentration of midazolam for amnesic benefit. The authors describe their anecdotal experience of patients using PCS who had a tendency for smaller doses of propofol and subsequently a reduced recovery time to satisfy discharge criteria. A total of 40 patients undergoing third molar extractions were randomly allocated to each group with the objectives of the study to measure the total dose of propofol used by each group and to assess recovery and patient satisfaction. The definition of desaturation was SpO_2<94% breathing room air and supplemental oxygen was not routinely administered. There was a very significant (p=0.00007) reduction in propofol dose in the PCS group (129mg) compared to the TCI group (216.4mg). Only one desaturation to SpO_2 was observed to 93% at 10 minutes in the TCI group and a significant difference in oxygen saturations noticed only at 5 minutes, where the mean SpO_2 in the TCI group was 96.85% compared to 97.7% in the PCS group (p=0.04). Performance tests to assess cognitive function, measure attention span and psychomotor function were assessed using three tests including sentence verification, letter search and maze task respectively. Only the psychomotor test showed that the TCI group were more sedated. Five patients demonstrated clinical signs of over sedation in the TCI group whereby verbal contact was lost, one failed to respond to verbal commands to open their mouth for administration of local anaesthetic. The authors surmised that in these cases, the one-minute induction time was too short and that the target blood concentration may be too high. The question of synergistic action between propofol and midazolam was postulated to be a contributing factor but no patient required supplemental oxygen or suffered airway obstruction. The study concluded that propofol preceded by a small dose of midazolam (0.03mg/kg) produced “safe, acceptable sedation” in their study population without impingement on psychomotor function.

2.6 Benefits of multi-drug sedation for patients & surgeons

There are two commonly quoted, desirable expectations expressed by patients when discussing pharmacological management for surgery. These are to have no recollection of the procedure and for the dental treatment to be pain free. On the other hand, operators are more likely to perceive the benefits as less behavioural interruption from the patient to facilitate successful completion of the surgery. There is a clinical perception that the combination of opioids and benzodiazepines result in increased patient cooperation and can help to reduce recovery time. The benefit to be attained, whether from the patient or operator perspective must be justified to warrant the increased risks on cardiorespiratory stability due to the narrower safety margins.

Parworth et al.[55] investigated safety and efficacy of midazolam and fentanyl compared to propofol and fentanyl in 57 patients undergoing third molar surgery between the ages of 16 and 40 years. The operating surgeon and observer were unblinded, however the patient was blinded to sedative drugs. Each study participant completed a 'Corah anxiety scale' pre-operatively and post-operatively, however these values were not found to be significantly different post operatively. The degree of amnesia was assessed using pictures shown during the procedure and recall of actual clinical events. Recall was reduced for those who had received midazolam and fentanyl (37.7%). The propofol and fentanyl group were rated to be significantly less co-operative (more talkative and disorientated) by an unblinded observer at five and fifteen minutes intra-operatively compared to those sedated with intravenous midazolam and fentanyl.

Dionne and Miller, Bullard and Patrissi[79] suggested that use of an opioid decreased the dose of benzodiazepine required to achieve the sedation target. As benzodiazepines are heralded for their amnesic and anxiolytic properties Milgrom et al. postulated that this reduction in midazolam dose may be associated with less relief of anxiety and shorter duration of amnesia. Ochs et al. [81] found that the addition of fentanyl to midazolam or diazepam was associated with little effect on the degree of amnesia experienced by 80 patients undergoing intravenous sedation for third molar extraction in a double-blind parallel group study[80].

The quality of sedation was graded on a four-point scale from poor to excellent at one time point, either at 30 minutes or at the end of surgery by a blinded, trained observer in Milgrom's study[52]. Both the independent, blinded observer and the operator's ratings of sedation quality were highly correlated. Patients who received a combination of midazolam and fentanyl were found to be four times more likely to rate their sedation as excellent compared to good, fair or poor sedation at a given level of intraoperative pain. The observer reported better sedation in the midazolam and fentanyl group with less movement and fewer verbalizations by the patient indicating upset. However patients did not report greater relief of anxiety or pain compared to midazolam alone. There was no evidence to support that multi-drug sedation raised the pain threshold, with no difference in self-reported pain at 5 and 15 minutes. This also extends the work of Khader who failed to find a significant difference in pain scores twenty-four hours post-operatively between single and multi-drug techniques.

The pain scores for subjects undergoing third molar removal in Goktay's study[48] were measured using the visual analogue sale at 0.5, 1, 4, 12 and 24 hours post-operatively and were found to be significantly different at one hour post-operatively only. Study participants who underwent intravenous sedation with midazolam only had significantly greater total analgesic drug consumption at the end of the seventh post-operative day, compared to the two drug groups combining midazolam with fentanyl or tramadol. The authors discussed that this may have been attributed to the efficacy of fentanyl and tramadol contributing to post-operative pain control. There was no difference between surgeon satisfaction among these three groups and all of the patients in each of the groups reported they would prefer to receive the same type of sedation and operation in the future.

2.7 Complications of multi-drug sedation

Conscious sedation providers must perform careful patient selection with a thorough pre-sedation assessment. Despite the infrequent reporting of adverse outcomes, it would be remiss to consider conscious sedation as being risk free as adverse events have the potential to arise from compromise of respiratory and cardiovascular systems.

Safety of conscious sedation in the outpatient dental environment is paramount. Outcome safety measures that are often reported across conscious and procedural sedation literature include quantification and description of adverse events. The lack of such events reported within dental sedation is attributable to multifactorial safety provisions including accredited post-graduate training programmes supported by supervised logbook of cases, engagement in continued professional development, thorough pre-assessment procedures and restricting sedation to only ASA I and II patients by the operator-sedationist in outpatient dental facilities. The sedation techniques adhere to titration of sedative drugs to an observed clinical end-point, continuous monitoring of vital signs with early interventions at predefined parameters. The standard, single-drug midazolam technique carries a wide safety margin which enables sedationists to confidently achieve the moderate target on the sedation continuum. However the synergistic action of opioids and benzodiazepines requires increased vigilance and caution to avoid overshooting the desired target on the spectrum.

Other potential complications with opioids include nausea and vomiting which are often related to the types of anaesthesia, surgery, dose and pain severity. Saiso et al. [50] specifically investigated the complications associated with intravenous fentanyl and midazolam sedation in patients undergoing minor oral surgery . The sample of patients included those under the age of sixteen and over the age of 65 with ASA I and ASA II patients contributing to 56.1% and 43.9% respectively. Complications developed in 11 patients (10.2%) without serious adverse events. Supplemental oxygen was delivered continuously to all patients at a rate of 3L/min via nasal cannula and 6 patients exhibited reduced arterial saturations of 95% which recovered with verbal stimulation. Two displayed deep sedation after failing to respond to verbal commands following initial doses, and paradoxical excitement was demonstrated by 1 patient. Only 1 patient reported nausea without vomiting and one had a prolonged recovery. Obesity was associated with a higher incidence of sedation related complications compared

to non-obese patients. When we compare this study protocol to our methodology, it is difficult to extrapolate these findings to our practice. Additional fentanyl and midazolam were administered intraoperatively to maintain a Ramsay score of 3-4, delivered by anaesthetists. We would consider this to extend further along the sedation continuum than would be acceptable practice of conscious sedation delivered by dental operator-sedationists in Ireland.

2.8 Advanced sedation techniques in the medical literature

Procedural sedation is routinely practiced for many types of medical procedures such as endoscopy, colonoscopy, gynaecology and in emergency departments. There is great variation in sedation techniques described, with no consensus on which is best. Many aspects of sedation with fentanyl and midazolam have been investigated in the medical literature including safety and effectiveness, patient and physician preferences, stability of vital signs and complications. There is great difficulty in drawing conclusions due to the heterogeneity of definitions of adverse events such as hypoxaemia and apnoea, as well as measuring non-standard end-points [(81)]. The dental sedationist should cautiously draw conclusions from these papers as the level of sedation is often targeted deeper on the sedation continuum depending on each country's international standard. A range of sedation depths are reported with patients drifting between moderate and deep sedation [(82)].

A large prospective series on the safety of intravenous midazolam and fentanyl was performed by Mamula et al. [(83)] involving a paediatric population in the United States undergoing gastrointestinal endoscopy with 1578 patients, all receiving 2L/min oxygen via nasal cannula. The safety of fentanyl and midazolam was measured in terms of the number of adverse events categorised on a scale of mild, moderate and severe. Adverse events were observed in 308 (19.5%) patients of which the majority were related to respiratory events. Apnoea was defined as a serious adverse event and occurred in 2 patients (0.2%). Desaturation below 92% more commonly lasted for less than twenty seconds in 100 patients (9%) compared to greater than twenty seconds in 12 patients (0.7%). Vomiting (5%), rash (0.7%) and agitation (1%) were also reported. Interventions were usefully described by the authors to manage the respiratory events which required increasing supplemental oxygen delivery above 2L/min, tactile stimulation in 16 patients, jaw thrust in 5 patients and bag and mask ventilation in 2 apnoeic patients. Flumazenil was used in 2 patients in the recovery period but the indication for this was not disclosed. Whilst this younger population is beyond the remit of our study, it is interesting to note that the extent of interventions required are within competencies developed during training of dentists for conscious sedation on accredited training programmes.

Barriga et al [(84)] assessed the adequacy of sedation for endoscopy based on the opinion of the patient and the endoscopist for midazolam only versus fentanyl and midazolam in a randomised controlled,

prospective study. The sedation was delivered by an unblinded endoscopist performing the procedure who decided when the end point was reached. A questionnaire was then answered by the endoscopist at the end of treatment and by the patient 24-72 hours post-operatively. The endoscopist perceived patients receiving multi-drug sedation to better tolerate the procedure, rating this as either 'excellent' or 'good' by 78.3% versus 55.8% in the midazolam only group (P=0.043). Whereas from the patient's perspective both types of single and multi-drug techniques allowed for the procedure to be well tolerated at 93% and 94% respectively (P=1). There was no significant difference between the patient groups regarding the degree of amnesia between the different techniques. No difference in pain was reported between the midazolam and midazolam with fentanyl groups, with both groups of patients experiencing minimal discomfort during endoscopy.

Khan et al. [85] performed a double-blind, randomised controlled trial to compare the effect of adding fentanyl to midazolam in upper endoscopy procedures with 68 patients randomised to the fentanyl group and 69 to the placebo (midazolam only) group. The study was powered to require 72 patients in each arm. Limited data is provided on the vital signs intra-operatively, but did identify only three transient drops in oxygen saturations < 90% occurring in the fentanyl and midazolam group only, with continuous delivery of supplemental oxygen at 2L/min. Minor complications in the midazolam group occurred with 1 patient vomiting and one other developing nausea. Sedation was rated on a five-point visual Likert scale independently by both the endoscopist and nurse who were blinded to which sedative was administered. They reported multi-drug sedation to be significantly better (P=0.003) in terms of less retching and better co-operation, whereas patients reported no difference in their level of satisfaction when the fentanyl group were compared to the placebo group (P=0.4). Neither was any difference found when patients were asked if they would be willing to repeat the procedure, with all patients reporting that they would.

Administration of midazolam with or without fentanyl was investigated in a blinded fashion in 50 patients undergoing lower-extremity angiography by Cragg et al. [86]. Average doses used were not comparable to that likely to be seen in dental sedation as greater amounts of fentanyl were delivered, with average doses of midazolam and fentanyl given at 2.9mg ± 1.3mg and 132.5 µg ± 45.2 µg respectively. Changes in oxygen saturation displayed a greater standard deviation from the mean in the midazolam and fentanyl group compared to midazolam alone, i.e. 95% ± 6% and 96% ± 2%

respectively. There was a small but significant decrease in blood pressure two minutes following the loading dose in both groups. The physicians involved were asked to provide their opinion immediately post-operatively. The effectiveness of midazolam and fentanyl sedation was judged to be superior than midazolam alone ($P<0.01$) observing patients to have significantly greater cooperation. Patients were also found to agree with physicians, rating the effectiveness of midazolam and fentanyl to be superior with greater anxiolytic effects ($P=0.0134$). However it is worth bearing in mind that baseline data reported that twice as many patients in the midazolam only group were reported to be relaxed before the procedure.

The haemodynamic and sedative effects on patients undergoing coronary angiography was investigated in a prospective, double blind, randomized study by Baris et al. [87] in patients receiving midazolam with or without fentanyl or placebo (local anaesthetic only) in 90 patients. The authors concluded that haemodynamic stability was greater in patients with sedation versus those who underwent the procedure with local anaesthetic alone. Both sedation techniques were found to be satisfactory according to both patients and cardiologists in terms of sedation scores and anxiolysis with no difference between the groups.

The applicability of results from research involving procedural sedation is useful, but is limited by low specificity where the assessment of hypoxaemia has not been the primary outcome of investigation. The validity of changes in haemodynamics are limited due to varying doses and techniques of drug administration. It is impossible to make inferences of the incidence of hypoxaemia as supplemental oxygen is routinely given, acknowledged to be a constituent of many medical specialty guidelines for procedural sedation. The lack of difference perceived by patients between midazolam with or without fentanyl is worth noting. Whilst there appears to be a trend among the healthcare professionals for the combining an opioid with a benzodiazepine, the reported patient experience does not convincingly distinguish an additional benefit.

2.9 Summary of literature review

There is a lack of research to quantify the incidence of hypoxaemia with intravenous fentanyl and midazolam sedation in the context of oral surgery procedures. Studies which do report on this outcome executed their methodology at variance to the typical conscious sedation procedure performed in the outpatient oral surgery setting in Ireland and the UK. From the literature review, the study exhibiting the greatest external validation to our practice from Goktay did not observe any desaturations below SpO_2 98%, however this outcome was measured at intervals rather than via continuously generated data. There is a need for an investigation to be conducted in line with the methodology generally practiced in oral surgery departments which includes an initial bolus dose of fentanyl, followed by titration of midazolam to the clinically determined end-point. There is a deficiency in the research methodology for sedation to be delivered by an oral surgeon acting as an operator-sedationist, without the routine use of supplemental oxygen and monitoring with pulse oximetry alone.

There is yet to be a sufficiently powered study to primarily investigate the onset of hypoxaemia with intravenous fentanyl and midazolam. Much of the published literature assesses multiple quantitative and qualitative outcomes and could be potentially criticized for dredging the data in order to produce statistically significant results for publication. One advantage offered by the medical literature is the larger numbers of participants involved within the studies. Sample sizes in the dental literature are more often quoted in the "tens" of patients which limits extrapolating these results to the wider population. The increased frequency of hypoxaemia and apnoea has been well reported in the medical literature on procedural sedation. The results from this literature review on the dental evidence base identifies consistent reports of adverse respiratory effects including hypoxaemia and apnoea which are transient in nature and recover with minor interventions. This reinforces confidence in the safety of performing our investigation in the oral surgery department as the rescue procedures are within the capabilities of appropriately trained dental sedationists.

Risk factors for hypoxaemic events are poorly reported and there is a need to provide further clarification on characteristics of at-risk patients, particularly when opioid and benzodiazepines are employed.

Anaesthetic colleagues have been dubious of dental practitioners in primary care embarking on multi-drug sedation techniques. The rigorous education of dentists with logbooks of supervised cases on validated training programmes often exceeds the training undertaken by other medical specialties involved in procedural sedation. This has been postulated to account for the low numbers of reported adverse events for sedation in dentistry compared to those observed in other medical specialties. Dentistry appears to be under greater scrutiny, with a greater mountain to climb for endorsement by anaesthetics, particularly with regards to the sole clinician in an operator–sedationist role. This highlights the need for good quality research so we can identify our hypoxaemic rate and further assess whether our current methodology is sufficient, such as the monitoring procedures and practice of withholding supplemental oxygen.

Research in advanced sedation techniques in dentistry has been shown to be a contentious issue, stimulating much debate towards researchers pushing the boundaries in an attempt to find suitable alternatives to DGA when standard sedation procedures fail. The use of multiple inhaled sedative agents and/or combinations of intravenous sedatives has led to criticism of exposing patients to unnecessary risk. Guidelines pioneered by 'A Conscious Decision' have been working earnestly to steer dentistry away from sedation procedures with greater inherent risk. The combined analgesic and anaesthetic potential of fentanyl and midazolam is potentially least vulnerable to criticism as trained dental sedationists are already comfortable with titrating midazolam to effect. With appropriate training in advanced techniques, dental sedationists can be informed of the heightened vigilance required for the synergistic interaction between fentanyl and midazolam. This may be a more acceptable technique to meet requirements for anxiolysis between single drug midazolam and DGA, compared to other advanced techniques in the dental literature which are limited by the need for anaesthetic-led sedation due to the sedatives employed in primary care.

3. Methodology

There is a paucity of evidence in the dental literature primarily investigating the incidence of hypoxaemia in ASA I & II patients undergoing advanced sedation procedures employing the combination of an opioid and benzodiazepine. This investigation was performed on the context of ambulatory procedures within the Oral Surgery outpatient department in Cork University Dental School and Hospital. This research will usefully contribute to the small body of evidence currently available, being the first prospective study to assess the onset of hypoxaemia in single operator-sedationist conscious sedation with intravenous fentanyl and midazolam.

Ethical approval

CREC Review Reference Number: ECM 4 (q) 03/12/19.

The "Clinical Research Ethics Committee of the Cork Teaching Hospitals" (CREC) approved the research protocol in its original format in December 2019 (Appendix 1). The study commenced in January 2020 and was completed over a twelve-month period and was conducted in line with ethical principles as outlined by the World Medical Association Declaration of Helsinki [88]. There were no changes to the study protocol requiring resubmission to CREC for the duration of the investigation.

3.1 Aims

The primary aim of this prospective observational study is to measure the incidence of hypoxaemia in adult patients undergoing conscious sedation with intravenous fentanyl and midazolam for oral surgery procedures. The severity of hypoxaemia was graded on the three-point scale according to the following parameters [89]:

- Mild hypoxaemia: SpO_2 93-94%
- Moderate hypoxaemia: SpO_2 90-92%
- Severe hypoxaemia: SpO_2 <90%

The secondary aims were to identify the most likely time that a hypoxaemic event occurs relative to the first increment of fentanyl and to categorize this according to the stage of procedure. The data were assessed to determine any significant risk factors associated with hypoxaemia such as age, sex, BMI, ASA, smoking status and dose of midazolam.

3.2 Power calculation

To determine the expected incidence of hypoxaemia below 94% with IV fentanyl and midazolam, research from the existing body of literature was considered where supplemental oxygen was not routinely used and hypoxaemia was defined as SpO_2 <95%. The small pool of available evidence with heterogenous methods are arguably too precarious to infer an estimated incidence for this study. As outlined in the literature review, only two studies did not administer supplemental oxygen routinely to their subjects; Goktay did not observe any desaturations less than 98% [48], whereas Garip's study on patient-controlled sedation with remifentanil and midazolam observed 10 subjects (50%) desaturating to less than 95% [47].

To date, there is only one study in the literature which reliably demonstrates the greatest external validation to align with this study protocol, performed in the Oral Surgery Department in Cork. The primary aim of this study was to determine if the addition of microstream capnography to standard monitoring resulted in a decreased incidence of hypoxaemia during conscious sedation [46]. Supplemental oxygen was only administered if a patient failed to maintain their saturations above 94% and hypoxaemia was defined as $SpO_2 \leqslant 94\%$. Of the 190 participants, 70 developed an episode of hypoxaemia (36.8%). This result was used to inform the estimated rate of hypoxaemia in this study to be 40%, owing to the increased risk of respiratory suppression due to the synergistic action of fentanyl and midazolam. To achieve a power of 80% at the 5% significance level (2-sided test with 95% confidence interval) a sample size of 92 patients was calculated to allow an assumed rate of hypoxia at 40% with a 10% margin of error.

3.3 Study participant recruitment

Patients attending CUDSH Oral Surgery department for procedures under conscious sedation were invited to participate in this study following assessment for suitability and informed consent. Patients were identified from the conscious sedation waiting list which is populated from referral sources including general dental practitioners, the emergency dental clinic in CUDSH and internal referrals from other dental hospital departments. Additionally a review of the general anaesthetic waiting list was performed with re-evaluation of clinical records to identify potential patients that could be suitably transferred to the conscious sedation waiting list.

Inclusion criteria:

- Conscious sedation indicated due to patient anxiety or complex nature of surgical procedure
- ASA I& II
- BMI $\leqslant$ 35
- Age range between 18 and 65 years
- Absence of respiratory disease

Exclusion criteria:

- ASA > II
- Pregnancy/lactation
- Allergy to sedative medications
- Chronic use of CNS depressants
- Current use of opioids
- Premedication

Consultation and pre-assessment

Routine initial consultation was performed, exploring the presenting complaint, ascertaining the medical, dental and social history, clinical examination, diagnosis and discussion of treatment options with relative risks and benefits. Upon discussion of the various treatment modalities, when a patient opted for treatment under conscious sedation, a pre-assessment was performed with our registered general nurse.

A standard pre-assessment proforma was completed for every patient in line with guidance from SDCEP and IACSD. To assess the suitability for conscious sedation in the outpatient department the RGN made further enquiries into previous medical, surgical and anaesthetic history, calculation of body mass index and recorded baseline vital signs (SpO_2, HR and NIBP) and ASA classification documented. Providing suitable pre-assessment result and inclusion criteria were satisfied, the patient was offered the opportunity to enroll in the study. Discussion of the study was supported by allowing the patient time to read the CREC approved research information, which some opted to take home for further consideration (Appendix 2). The level of each individual's dental anxiety was ascertained by completing the 'Modified Dental Anxiety Scale' questionnaire (Appendix 3) providing anxiety characteristics of the study population [(90))]. Pre and post sedation instructions were given at the assessment appointment to ensure the patient was appropriately prepared for their sedation appointment. First stage consent was completed to satisfy all the components of informed consent and an appointment was given to the patient before leaving the department.

3.4 Study protocol

The timeline for data collection coincided with the instigation of new COVID protocols in our clinics. One day prior to patient attendance, a dental nurse performed a phone call triage to contact each study participant regarding a COVID clearance questionnaire before confirming the appointment. Each escort presented to the main reception to confirm their attendance with the patient, contact details were taken and the escort asked to wait either in their car or socially distanced waiting room.

Pre-op preparation

The study participant was initially brought into a non-clinical room where details of the sedation pre-assessment was checked, vital signs taken again and compared to baseline vitals at initial consultation. Any change to the planned procedure was updated on the consent form prior to confirming second stage consent. Once completed, the patient was guided into the sedation suite and positioned in the dental chair and introduced to the clinical and research team consisting of:

- Operator-sedationist: Two specialist oral surgeons who hold qualifications in conscious sedation with training and experience in advanced sedation techniques
- Dental nurse to assist the surgery
- Un-scrubbed dental nurse to assist with any instrument or equipment requirements
- Sedation trained nurse acting as the 'second appropriate person' to monitor the sedated patient
- Research investigator overseeing adherence to the research protocol, performing data collection, but did not participate in the surgical procedure.

Once the patient was seated in the dental chair, the research investigator attached the monitoring equipment and commenced gathering five minutes of baseline data. The sedation monitor used in this study was the 'BeneVision N12 Mindray', provided by NORSO medical who did not have any participation in the study. During the five-minute monitoring time, the WHO Surgical Checklist [91] was performed and a 22-gauge peripheral cannula was placed in the right dorsum of the hand or antecubital fossa, flushed with 0.9% saline and secured in place with a tegaderm dressing. To prevent

interference in gathering baseline pulse oximetry data during placement of the intravenous cannula, the finger probe was switched temporarily from the right index finger to the left index finger.

Monitoring equipment

The following monitors were attached to every sedation patient and connected to the Benevision monitor (Figure 4):

- Pulse oximeter to right index finger
- Blood pressure cuff on left arm
- Smart CapnoLine specialized oro-nasal cannula: Cannula placed into the nostrils with an attached oral component positioned just inferior to the upper lip to catch external breath from both the nose and mouth.

Figure 4: Demonstration of patient with sedation monitoring equipment.

Drugs for sedation

The sedative medications were removed from a locked cupboard at the point of use and the corresponding logbooks were updated to maintain an accurate record study participant's name and hospital number, as well as a tally of remaining drugs. Fentanyl and midazolam were supplied as:

- Hypnovel 10mg Solution for injection. Midazolam 10mg/2ml.
- Sublimaze 2ml. Injection fentanyl (as citrate). Fentanyl 50µg/1ml. 100µg.
- Water for injection Ph. Eur. Solvent for parenteral use IV 10ml.
- 0.9% w/v Sodium Chloride Injection BP. For IV, IM or SC injection 10ml. (Figure 5)

Figure 5: Vials of fentanyl, midazolam, water for injection and saline from supplier.

The date and batch numbers of each vial of fentanyl, midazolam, water for injection and saline were checked by both the RGN and research investigator as well as the reversal drugs naloxone and flumazenil. The reversal protocol for use of the sedative antagonists was clearly displayed in the surgery. Responsibility for preparing each syringe of medication was held by the research investigator who prepared every syringe to maintain consistency (Figure 6):

- 0.9% NaCl:

  10ml drawn into a syringe and labeled with a white saline sticker.

- Hypnovel 10mg/2ml:

  Entire 2ml drawn into a 10ml syringe with 8ml of water for injection achieving a concentration of midazolam 1mg/ml and labelled with an orange midazolam sticker.

- Fentanyl 100µg /2ml:

  1ml (50µg) of solution drawn into a 2ml syringe and labelled with a blue fentanyl sticker.

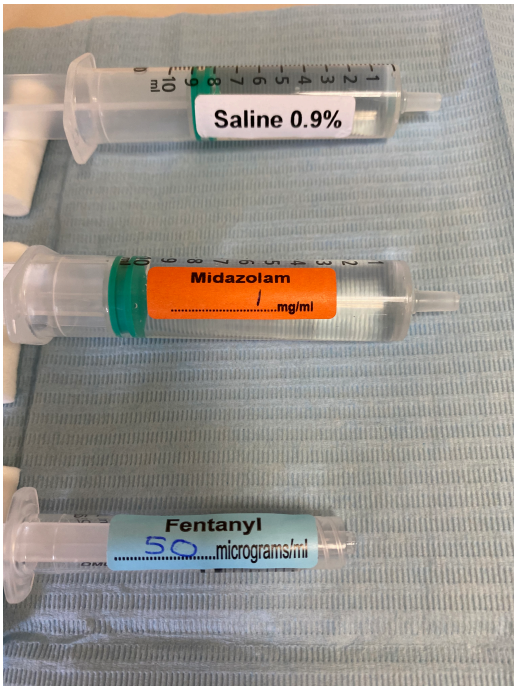


Figure 6: Prepared syringes for intravenous delivery by research investigator.

After the baseline data had been collected, the operator-sedationist administered a standard dose 1ml (50µg) of fentanyl via the peripheral cannula, followed by a saline flush. For consistency, all times were taken from the Benevision monitor. One minute after the fentanyl bolus, 1mg of midazolam was administered and titrated to patient response in increments of 1mg per minute until the operator-sedationist decided the sedation end point was achieved, coincident with an RSS score of 3.

A forty-minute monitoring period was permitted to detect the occurrence of hypoxaemia from the sedation end point. This time was determined as the majority of minor oral surgery procedures would likely be completed within this timeframe and nowhere in the literature reported significant differences in arterial oxygen saturations beyond this time. The chair was then placed in a supine position for the duration of the forty-minute monitoring time or until the end of the operation if research monitoring time was exceeded. Achieving effective local anaesthetic (2% lignocaine, 1:80,000 adrenaline, Septodont) is an essential pre-requisite for treatment under conscious sedation and was given once the sedation end point was achieved. The efficacy of the local anaesthetic was assessed by verbal questioning and probing the oral mucosa with additional injections supplemented throughout the procedure as required by the patient. Additional increments of midazolam were given intra-operatively at the discretion of the operator-sedationist if they observed the patient to be under-sedated during the treatment.

3.5 Data collection

The research investigator maintained all the relevant data on a proforma (Appendix 4) and ensured no identifying credentials were collected. An anonymous study identification number was assigned in a consecutive order to each participant and demographic characteristics recorded including the age, sex, BMI, smoking status and the MDAS score.

The monitor was adjusted to display four parameters including the heart rate, SpO_2, respiratory rate and blood pressure (Figure 7). All vitals were collected at 5 second intervals with exception of blood pressure which was automated to take a BP measurement at ten-minute intervals. The capnography waveform was hidden from the display to prevent bias in anticipating any observed hypoxaemia to be detected by the pulse oximeter.

Figure 7: BeneVision N12 Mindray display monitor.

A contemporaneous record of event times was recorded in order to accurately label the data once extracted from the monitor:

- Baseline data (5-minute period)
- First dose of fentanyl
- First dose and subsequent increments of midazolam
- Sedation end point

The pulse oximeter alarm was set at 90% and the research investigator was responsible for calling the patient to take a deep breath when a desaturation to SpO_2 94% was observed. If the patient failed to respond in a timely manner to verbal stimulation, then physical stimulation by means of a mild shoulder shake was instigated to stimulate increased respiratory drive. If the operator-sedationist felt the oxygen saturation was not improving, supplemental oxygen was administered via an additional port on the oro-nasal cannula (Smart CapnoLine) and an airway maneuver (head-tilt and chin- lift) was performed if required (Figure 8).

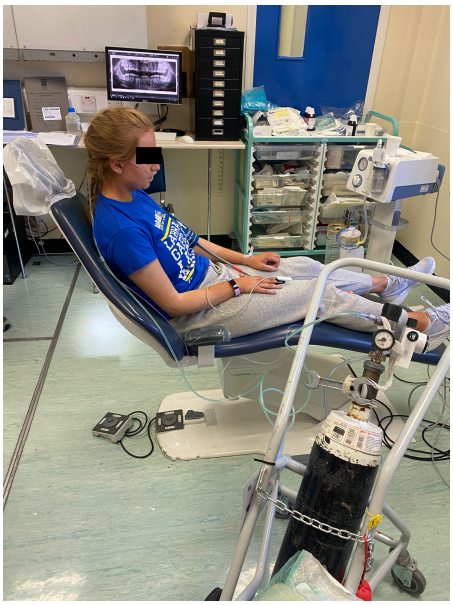


Figure 8: Supplemental oxygen attached to Smart CapnoLine monitor.

The antagonist drugs were readily available in the surgery if the patient became uncooperative or unresponsive, however at no point where they required. The research investigator recorded each episode of hypoxaemia and the maximum level of intervention required to correct the oxygen saturation along with:

- Time of hypoxaemic event
- Stage of procedure i.e. baseline monitoring, induction, pre-op, intra-op or post-op
- Severity: mild (93-94%), moderate (90-92%) or severe (<90%)
- Intervention performed to reverse hypoxaemia

The research investigator was present for every encounter to oversee correct execution of the study protocol and to record data applicable to the investigation. The times of any aberrant readings on any given monitor were noted on the data collection proforma, such as a dislodged pulse oximeter not detecting SpO_2, pulse oximeter unintentionally left on same hand as BP cuff or dislodgement of the oro-nasal cannula during the procedure. A record of these instances was required to facilitate 'data cleaning' post-hoc to ensure erroneous data was excluded from the analysis.

The protocol aimed to maintain and achieve an RSS score of 3 and was quantified at two time points from the beginning of the operation i.e. at 5 and 15 minutes from the beginning of the operation as referenced in previous studies[55]. The intention was to show consistency of the level of sedation over the course of the study and to indicate any deviations of under-sedation or over-sedation which may contribute to an increased incidence of hypoxaemia.

At the end of the procedure the operator-sedationist was asked to grade the operating conditions to determine their assessment of the patient's level of co-operation for surgery under sedation:

1. Good: Patient fully co-operative with optimum degree of sedation
2. Fair: Minimal interference from patient due to over/under sedation
3. Poor: Operating difficult due to over/under sedation
4. Impossible

Monitoring equipment was only removed at the end of the research interval or end of operation for transfer to the recovery room. The patient was observed in recovery and a record maintained of their vital signs. When deemed suitable for discharge, the peripheral cannula was removed and the escort was brought to the recovery room for delivery of post-operative instructions relating to sedation and the operation, supported with a written copy. No data from recovery was required for this study and no follow up was required relative to the sedation unless otherwise indicated for the surgical procedure.

Data Retrieval

Each data set was transported via memory stick from the 'Benevision Monitor' to a laptop with installed 'BeneVision CMS Viewer' (system software version V07.20) (Figure 9). This program enabled the data to be reviewed and exported directly to a 'Microsoft Excel' file. Each data set was exported from the CMS viewer into Excel and saved under the anonymous study identification number.

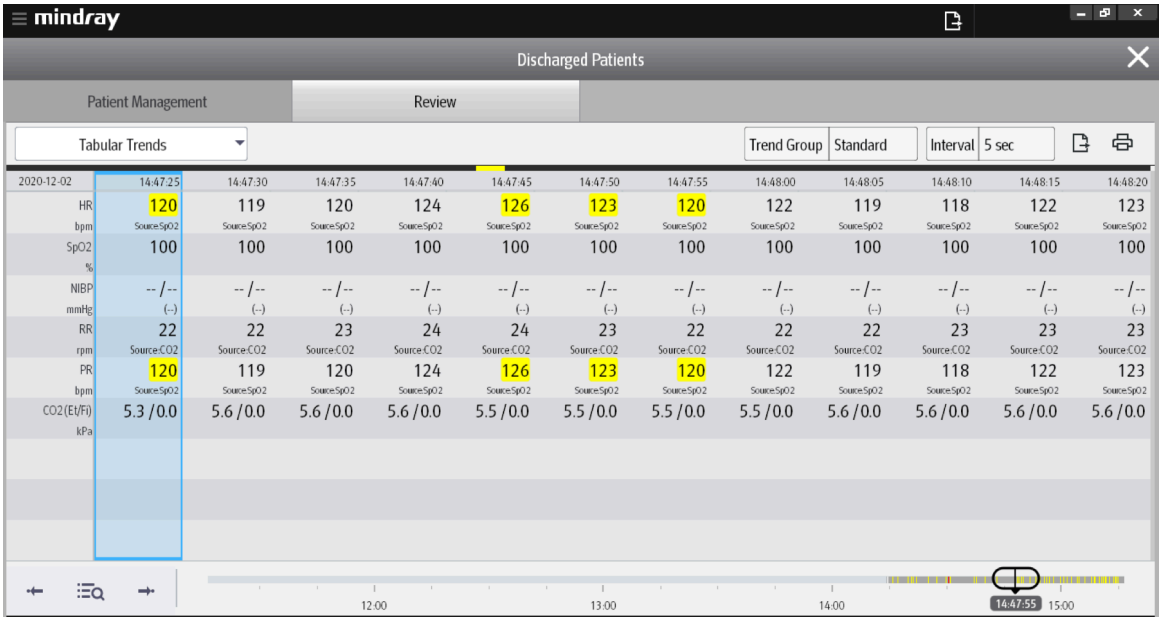


Figure 9: Data imported to CMS viewer.

Each data set was reviewed alongside the data collection proforma and labelled with the time for baseline monitoring, first dose of fentanyl, first and each subsequent doses of midazolam during induction, end point, any further increments of midazolam (with respective dose) and end of monitoring time. Any data beyond the end of monitoring time was maintained to the end of the operation. With reference to the hand-written record in real time of aberrant readings occurring intra-operatively, the data was reviewed to replace anomalous readings with a full stop (Figure 10).

Time	HR(bpm)	SpO2(%)	NIBP-S(mmHg)	NIBP-D(mmHg)	NIBP-M(mmH	RR(rpm)	EtCO2(kPa)	
8/19/20 9:42	69	100	–	--	--	31	2.9	
8/19/20 9:42	69	100	–	--	--	24	3.7	
8/19/20 9:43	69	100	–	--	--	24	3.6	
8/19/20 9:43	69	100	–	--	--	21	3.7	
8/19/20 9:43	63	99	–	--	--	21	3.7	
8/19/20 9:43	.	.	–	--	--	20	3.6	
8/19/20 9:43	.	.	–	--	--	19	3.6	
8/19/20 9:43	.	.	–	--	--	18	3.7	
8/19/20 9:43	56	99	–	--	--	17	3.7	
8/19/20 9:43	57	99	–	--	--	16	3.7	
8/19/20 9:43	54	99	–	--	--	16	3.7	
8/19/20 9:43	55	100	–	--	--	16	3.7	
8/19/20 9:43	60	100	–	--	--	16	3.7	
8/19/20 9:43	60	99	–	--	--	15	3.7	
8/19/20 9:44	59	99	–	--	--	14	3.7	Fentanyl 50mcg
8/19/20 9:44	60	99	–	--	--	14	3.7	
8/19/20 9:44	60	99	–	--	--	14	3.7	
8/19/20 9:44	62	99	–	--	--	14	3.6	
8/19/20 9:44	68	99	–	--	--	17	3.5	
8/19/20 9:44	71	99	–	--	--	24	3.3	
8/19/20 9:44	73	99	–	--	--	23	3.5	
8/19/20 9:44	72	99	–	--	--	22	3.5	
8/19/20 9:44	75	99	–	--	--	23	3.5	
8/19/20 9:44	74	99	–	--	--	31	3.3	
8/19/20 9:44	71	100	–	--	--	32	3.3	
8/19/20 9:44	68	100	–	--	--	32	3.3	
8/19/20 9:45	68	99	–	--	--	27	3.6	Midazolam 1mg
8/19/20 9:45	67	99	–	--	--	22	3.6	
8/19/20 9:45	65	99	–	--	--	18	3.7	
8/19/20 9:45	65	100	–	--	--	18	3.7	
8/19/20 9:45	66	99	–	--	--	14	3.7	
8/19/20 9:45	66	100	–	--	--	13	3.7	
8/19/20 9:45	66	100	–	--	--	14	3.7	
8/19/20 9:45	67	100	–	--	--	16	3.7	
8/19/20 9:45	73	99	–	--	--	17	3.7	
8/19/20 9:45	75	99	–	--	--	19	3.7	
8/19/20 9:45	76	99	–	--	--	18	3.7	
8/19/20 9:45	72	99	–	--	--	15	3.7	
8/19/20 9:46	70	99	–	--	--	16	3.6	Midazolam 2mg

Figure 10: Data exported to Microsoft Excel for "data cleaning".

3.6 Statistical methods

All statistical analyses were performed in SAS® (Version 9.4). The level of significance used in all statistical tests was 5%. The severity of hypoxaemia was graded on a three-tiered scale with the following parameters:

- Any hypoxaemia: ≤94%
- Moderate hypoxaemia SpO_2 90-92%
- Severe hypoxaemia SpO_2 <90%

A plot of SpO_2 readings over the forty-minute monitoring period was produced for each study participant accurately demonstrating the changes in arterial oxygen saturations over the course of treatment. Three horizontal lines on the plot represent the tiers of hypoxaemia severity to illustrate when each parameter of hypoxaemia was encountered (Figure 11).

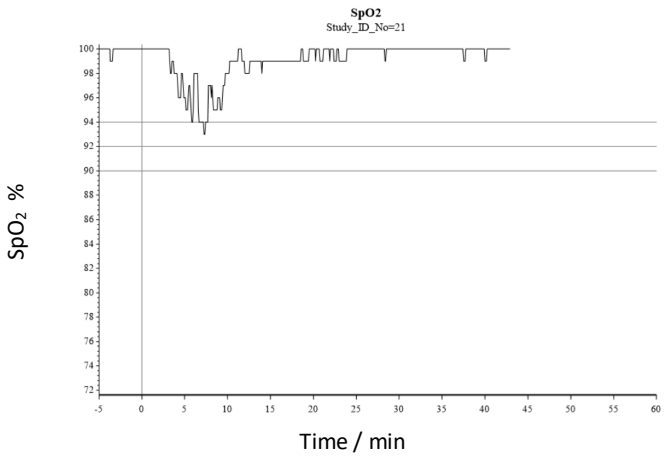


Figure 11: Graph plotting SpO_2 readings from baseline monitoring to end of monitoring/treatment time.

Multivariate logistical regression analysis assessed for significant associations between variables including a range of patient demographics, vital signs, doses and timing of intravenous medications and sedation scores.

4. Results

Patients referred to the oral surgery department for treatment under conscious sedation were prospectively recruited to this study with a total of 96 patients consenting to participate in the research study. The first two data sets were lost due to a problem in data transfer from the Benevision monitor to the computer software CMS viewer and therefore were excluded from the study. A total of 94 patients were included in the data analysis. All patients successfully completed their intended treatment plan with no sedation failures. All patients remained conscious and responsive to instructions with no requirement for any reversal of sedation.

4.1 Demographics

The average age of study participants was 31.8 years (SD 12.8), ranging from 16 to 65 years with a slightly greater representation of females (n=55) compared to males (n=39) recruited to the study (Table 4).

Table 4: Sex of study participants.

Sex	n	%
Female	55	59
Male	39	41

Each patient was assigned to a 'American Society of Anaesthesiology - Physical status' category during the pre-assessment for sedation. The vast majority were categorised as ASA I, healthy, non-smokers and just over a third identified as ASA 2, having mild systemic disease and/or a smoking habit. The study population were strongly represented by non-smokers (83%) (Table 5).

Table 5: Proportion of ASA categories and smoking status.

Variable	Category	n	%
ASA	1	60	64
	2	34	36
Smoker	No	78	83
	Yes	16	17

A good spread of BMI values was included with an average of 25.8 kg/m^2 (SD 4.2), minimum of 17.8 kg/m^2 and a maximum BMI of 36.2 kg/m^2.

Modified Dental Anxiety Scores

All participants completed the modified dental anxiety scale (MDAS) at the time of consenting to participation in the study. The lowest score possible is 5 indicating no anxiety and the maximum score is 25, with a benchmark at 19 or above representing an extremely anxious patient who is possibly phobic. The average MDAS score of the 94 participants was 13.8 (SD 5.5) with a range of scores between 5 and 25.

Indication for sedation and surgery performed

There were three broad indications for conscious sedation including patient's preference for anxiolysis, recommendation by surgical team based on invasive nature of surgical procedure and for relaxation of a strong gag reflex (Table 6). A wide variety of oral surgery procedures were performed under sedation demonstrating the versatility granted with combined opioid and benzodiazepine

sedation (Table 7). Autogenous cortical bone grafts including the mandibular ramus and symphyseal donor sites were harvested in a procedure typically reserved for general anaesthetic. However with correct patient and surgery selection we were able to perform these safely in the outpatient department, capitalizing on the advanced sedation technique.

Table 6: Indication for treatment under conscious sedation.

Indication for sedation	n	%
Anxiolysis	74	79
Invasiveness of surgical procedure	19	20
Gag reflex	1	1

Table 7: Frequency of Oral surgery procedures performed under conscious sedation.

Surgical procedure	n	%
Surgical extraction	52	55.3
Forceps extraction	19	20.2
First stage implant placement	5	5.3
Removal of infected mandibular fixation plate	5	5.3
Coronectomy of mandibular third molar	3	3.2
Autogenous mandibular/maxillary bone graft	3	3.2
Apicectomy	2	2.1
Second stage implant placement of healing abutment	1	1.1
Removal of failed osseointegrated implant	1	1.1
Removal of hyperplastic tissue	1	1.1
Closure of oro-antral fistula	1	1.1
Removal of bony sequestrum (mandibular osteomyelitis)	1	1.1

Baseline vital signs

Baseline vital signs were monitored for five minutes prior to the administration of any intravenous agent. In five patients, the baseline monitoring time was shorter due to a clinical recording error, with the minimum baseline time recorded being 3 minutes. The data in Table 8 illustrates the descriptive statistics of the baseline vital signs recorded for the study population.

Table 8: Baseline vital signs of all study participants.

Variable	min	max	mean	SD
SpO_2 (%)	95.7	100	99.3	0.8
Heart rate (BPM)	49.7	135.7	82.8	15.5
Systolic blood pressure (mmHg)	100.0	184.0	134.8	16.1
Diastolic blood pressure (mmHg)	63.5	106.3	83.7	9.1
Mean blood pressure (mmHg)	71.0	133.0	98.8	12.0
Respiratory rate (breaths/min)	8.3	32.1	19.8	3.8
$EtCO_2$ (kPa)	1.79	5.26	4.00	0.61

4.2 Conscious sedation measures

Two oral surgeons were involved in delivery of intravenous sedation drugs to achieve a suitable end point, enabling the operative procedures to be completed with the required level of anxiolysis. Each specialist oral surgeon shared a fairly even proportion of procedures (Table 9).

Table 9: Number of sedation cases per each oral surgery specialist.

Oral Surgeon	n	%
Specialist 1	43	46
Specialist 2	51	54

Ramsay Sedation Scale Score

Sedation scores were graded at two time points during the sedation procedure, at five and fifteen minutes from the time of sedation end point (Table 10). In all cases, these scores were determined by the research investigator in accordance with the categories outlined by the Ramsay Sedation Scale.

Table 10: Frequency of RSS scores at 5 and 15 minutes.

RSS Score time from end point	RSS	n	%
5 minutes	1	4	4
	2	10	11
	3	80	85
15 minutes	1	2	2
	2	10	11
	3	82	87

Operating conditions

The operating conditions were graded at the end of the procedure by specialist 1 and specialist 2 based on their subjectivity of patient co-operation for the surgical procedure, given the quality of sedation displayed (Table 11).

Table 11: Operating conditions as graded by the operator-sedationist.

Operating Conditions	n	%
Good: Patient fully co-operative with optimum degree of sedation	83	88
Fair: Minimal interference from patient due to over/under sedation	10	11
Poor: Operating difficult due to over/under sedation	1	1
Impossible	0	0

Midazolam dose to endpoint

A consistent order of intravenous drug delivery was applied to each participant with an initial dose of 50µg fentanyl, followed one minute later with midazolam at a rate no greater than 1mg/min. On occasion the intervals for midazolam were greater than 1 minute as the sedationist required extra time to judiciously observe the clinical signs of sedation demonstrated by the patient to determine if another 1mg was required, in order to avoid over sedation. The average dose of midazolam to achieve the sedation end point was 5mg (SD 1.4) with a range of 2-9mg (Table 12). The average time to sedation end point was 5.16 minutes, ranging between 2-10 minutes.

Table 12: Frequency distribution of midazolam dose to endpoint.

Dose of midazolam to end point / mg	n	%
2	3	3
3	7	7
4	27	29
5	26	28
6	16	17
7	12	13
8	1	1
9	2	2

If a patient displayed signs of under-sedation intra-operatively to potentially prohibit successful treatment completion, the sedationist/operator determined if additional increments of midazolam should be administered to restore anxiolysis, aiming for RSS of 3. The majority of patients (n=81, 86%) did not require any further doses of midazolam, however 13 patients displayed features of under-sedation during their procedure and were given additional midazolam. The average dose of additional midazolam administered was 2.15 mg and the frequency of patients receiving the variable doses of intra-operative midazolam are provided (Table 13). The average MDAS score of patients requiring additional intra-operative midazolam was 15.2, 10% higher than the average MDAS score of the population overall.

Table 13: Frequency of patients requiring additional doses of midazolam intra-operatively.

Intra-operative midazolam / mg	n	%
0	81	86
1	6	6
2	3	3
3	2	2
4	0	0
5	2	2

4.3 Primary Objective: Incidence of hypoxaemia

The severity of the hypoxaemia was classified according to a three-tiered scale of mild, moderate or severe. The number of patients who developed any hypoxaemic event (SpO_2 ≤94%) was observed to be 50 out of the 94 participants (53%). Of the 50 patients that experienced 'any' hypoxaemia, 49 patients experienced 'mild' hypoxaemia first, some of whom went on to experience 'moderate' (32%) or 'severe' (20%) hypoxaemia, and 1 patient experienced moderate hypoxaemia only (Table 14). Thus, 'any hypoxaemia' is effectively 'mild hypoxaemia'.

An SpO_2 reading of 94% was an early warning sign to initiate verbal stimulation of the patient. This could have prevented patients experiencing moderate or severe hypoxaemia. Thus, the incidences of moderate and severe hypoxaemia and the times to these may be under-estimated.

Table 14: Incidence of hypoxaemia according to mild, moderate and severe parameters.

Hypoxaemia	**Yes**		**No**		**Total**
	n	**%**	**n**	**%**	
Any	50	53	44	47	94
Moderate	30	32	64	68	94
Severe	19	20	75	80	94

4.4 Secondary objective: Onset of hypoxaemia

Onset of first episode of 'any' hypoxaemia

The time to first onset of hypoxaemia was determined from the time of the first dose of intravenous drug i.e. 50µg fentanyl. On average, the time to first episode of hypoxaemia was 8 minutes, with a range between 0.7 – 43.3 minutes (Table 15). The earliest episode of hypoxaemia was observed to occur at 42 seconds, reflecting hypoxaemia related to intravenous fentanyl alone and the maximum time was 43.3 minutes (Figure 12). Overall, 90% of hypoxaemic episodes had developed within 13.6 minutes relative to first fentanyl dose (lower quartile 4.3 minutes, upper quartile 6.8 minutes).

Table 15: Time to onset of first hypoxaemic episodes from first dose of intravenous fentanyl.

Hypoxaemia	n	min	P_{10}	Q_1	Q_2	Q_3	P_{90}	max	mean	SD
Any	50	0.7	3.3	4.3	5.7	6.8	13.6	43.3	8.0	8.9
Moderate	29	2.7	3.3	4.0	5.4	6.8	8.2	43.5	6.8	7.3
Severe	19	3.5	3.5	4.5	6.4	7.0	8.3	31.0	7.2	5.9

Figure 12: Bar chart of time to first episode of 'any' hypoxaemia.

Stage of first hypoxaemic episode

The timing of hypoxaemic episode was also categorised into four stages relative to surgical procedure:

1. Induction: From first increment of fentanyl and midazolam titrated at 1mg/min to patient response until sedation end point achieved.
2. Pre-op: Period between end point and beginning surgical procedure.
3. Intra-op: Period between beginning and end of operation.
4. Post-op: Period from end of operation to 40 minutes from sedation end point.

The greatest frequency of hypoxaemic episodes occurred during the pre-operative phase, where two thirds of 'any' hypoxaemia was observed. Further to this, the induction period was associated with 22% of episodes, whist markedly less occurred with the onset of surgical stimulation in the intra-operative (10%) and post-operative (2%) periods (Table 16 & Figure 13).

Table 16: Frequency of first hypoxaemic episode categorised to stage of procedure.

Hypoxaemia	**Induction**		**Pre-op**		**Intra-op**		**Post-op**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any	11	2	33	66	5	10	1	2
Moderate	7	24	21	72	1	3		
Severe	3	16	15	79	1	5		

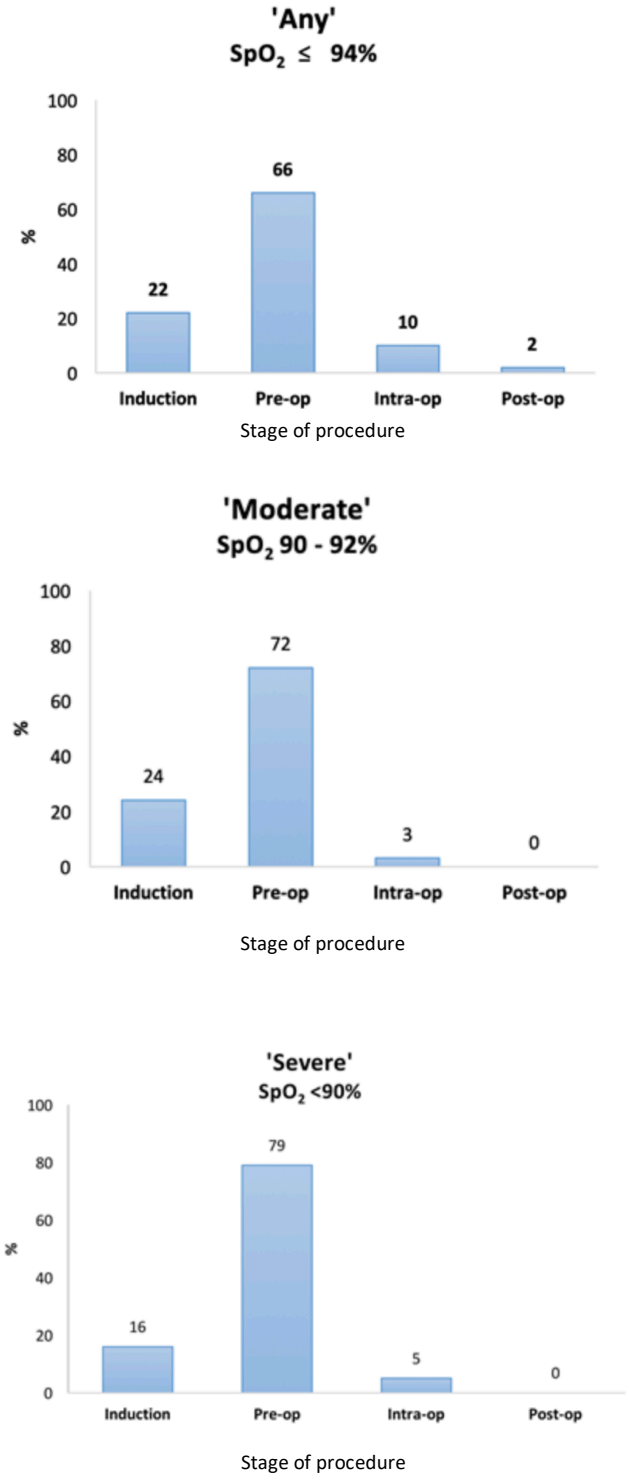


Figure 13: Bar charts representing frequency of hypoxaemic events according to stage of procedure.

4.5 Secondary Objective: Risk Factors for Hypoxaemia

Multivariate logistic regression analysis was performed to identify any risk factors associated with hypoxaemia. A comprehensive range of variables were assessed including patient demographics, vital signs and sedation measures. Each category of hypoxaemia severity was assessed to identify for any significant risk factors i.e. 'any', 'moderate' and 'severe' (statistical significance at the 5% level).

Risk Factors for 'Any' Hypoxaemia

Four variables achieved statistical significance for an increased risk of 'any' hypoxaemia including dose of midazolam to end point, baseline SpO_2, mean blood pressure and $EtCO_2$ (Table 17).

There was no association between age and hypoxaemia (p = 0.6306). Likewise, no significant difference was identified between sexes (p = 0.8912), BMI (p = 0.2209) or regarding smoking status (p=0.0587) for the occurrence of a hypoxaemic event.

The dose of midazolam required to achieve the sedation end point was associated with 'any' hypoxaemia (p = 0.0023), having a protective benefit. For each additional milligram of midazolam until the sedation end point, the risk of 'any' hypoxaemia reduced by 52% (95% CI: 0.30 - 0.77).

A number of vital signs were associated with 'any' hypoxaemia. The average baseline value was calculated for each of the vital signs for every individual patient. Baseline arterial oxygen saturation measured by pulse oximetry was significant for 'any' hypoxaemia (p = 0.0297), for each 1% lower than mean baseline SpO_2 the risk of 'any' hypoxaemia increased by 190% (95% CI: 1.11-7.59).

Similarly, the mean baseline blood pressure achieved statistical significance (p = 0.0235). Every 1 mmHg increase from baseline mean blood pressure resulted in an increased risk of 'any' hypoxaemia by 6% (95% CI: 1.01-1.12).

End tidal carbon dioxide was associated with 'any' hypoxaemia (p= 0.0203). For every 1 kPa lower than baseline $EtCO_2$, the risk of 'any' hypoxaemia increased by 192% (95% CI: 1.18. – 7.22).

Table 17: Multivariate logistic regression analysis for 'any' hypoxaemia.

Potential Risk Factor	Comparison (if categorical)	p-value	Odds Ratio	95% CI
Age		0.6306	1.01	(0.96, 1.07)
Sex	Female V Male	0.8912	1.09	(0.32, 3.76)
BMI		0.2209	1.07	(0.96, 1.18)
Smoker	Yes V No	0.0587	0.24	(0.05, 1.05)
Dose of Midazolam to endpoint		0.0023	0.48	(0.30, 0.77)
Time from 1st Midazolam to endpoint		0.4493	0.99	(0.97, 1.01)
Intra-op Midazolam	Yes V No	0.9594	1.03	(0.32, 3.34)
Operator	Specialist 1 V Specialist 2	0.9578	0.98	(0.43, 2.21)
Baseline SpO_2		0.0297	2.90	(1.11, 7.59)
Baseline HR		0.6204	1.01	(0.98, 1.03)
Baseline NIBP-S		0.8693	1.00	(0.97, 1.02)
Baseline NIBP-D		0.2606	1.03	(0.98, 1.08)
Baseline NIBP-M		0.0235	1.06	(1.01, 1.12)
Baseline RR		0.3173	1.07	(0.93, 1.23)
Baseline $EtCO_2$		0.0203	2.92	(1.18, 7.22)
MDAS		0.6602	1.02	(0.94, 1.10)
Ramsay 5 min	(1 or 2) v 3	0.3709	1.71	(0.53, 5.56)
Ramsay 15 min	(1 or 2) v 3	0.7028	1.27	(0.37, 4.33)
Operating Conditions	(Fair or Poor) V Good	0.4632	1.63	(0.44, 5.98)

Risk Factors for 'Moderate' Hypoxaemia

Age was the only clinical variable that was found to be a significant risk factor for 'moderate' hypoxaemia (p = 0.0003) (Table 18). For each year of additional age, the risk of moderate hypoxaemia increased by 7% (95% CI: 1.03 – 1.12).

Table 18: Multivariate logistic regression analysis for 'moderate' hypoxaemia.

Potential Risk Factor	Comparison (if categorical)	p-value	Odds Ratio	95% CI
Age		0.0003	1.07	(1.03, 1.12)
Sex	Female V Male	0.8823	0.91	(0.28, 3.03)
BMI		0.6882	0.98	(0.88, 1.09)
Smoker	Yes V No	0.5794	0.71	(0.21, 2.41)
Dose of Midazolam to endpoint		0.0790	0.69	(0.46, 1.04)
Time from 1st Midazolam to endpoint		0.3102	0.98	(0.95, 1.02)
Intra-op Midazolam	Yes V No	0.9945	1.00	(0.28, 3.54)
Operator	Specialist 1 V Specialist 2	0.5708	1.29	(0.53, 3.13)
Baseline SpO_2		0.7489	0.89	(0.44, 1.81)
Baseline HR		0.5041	0.99	(0.96, 1.02)
Baseline NIBP-S		0.3415	0.99	(0.96, 1.02)
Baseline NIBP-D		0.6997	1.01	(0.96, 1.06)
Baseline NIBP-M		0.7252	1.01	(0.97, 1.05)
Baseline RR		0.4361	1.05	(0.93, 1.18)
Baseline $EtCO_2$		0.1948	1.79	(0.74, 4.30)
MDAS		0.7082	1.02	(0.94, 1.10)
Ramsay 5 min	(1 or 2) v 3	0.2965	1.86	(0.58, 5.95)
Ramsay 15 min	(1 or 2) v 3	0.8421	1.14	(0.31, 4.14)
Operating Conditions	(Fair or Poor) V Good	0.7848	0.82	(0.20, 3.35)

Risk Factors for 'Severe' Hypoxaemia

In a similar finding to 'moderate' hypoxaemia, age was again identified as the only variable achieving the 5% significance level as a risk factor for 'severe' hypoxaemia (Table 19). Each additional year of age created an increased risk of 'severe' hypoxaemia by 8% (95% CI: 1.02 – 1.13).

Although female patients were 70% more likely to develop a 'severe' episode of hypoxaemia compared to males (95% CI: 0.58 – 4.96), this difference did not reach the 5% significance level to be identified as a risk factor (p = 0.3295).

Table 19: Multivariate logistic regression analysis for 'severe' hypoxaemia.

Potential Risk Factor	Comparison (if categorical)	p-value	Odds Ratio	95% CI
Age		0.0002	1.08	(1.02, 1.13)
Sex	Female V Male	0.3295	1.70	(0.58, 4.96)
BMI		0.6234	1.03	(0.91, 1.16)
Smoker	Yes V No	0.8730	0.89	(0.23, 3.52)
Dose of Midazolam to endpoint		0.1856	0.72	(0.44, 1.17)
Time from 1st Midazolam to endpoint		0.3680	1.00	(1.00, 1.01)
Intra-op Midazolam	Yes V No	0.2515	0.29	(0.04, 2.40)
Operator	Specialist 1 V Specialist 2	0.8736	0.92	(0.34, 2.53)
Baseline SpO_2		0.6971	0.87	(0.44, 1.73)
Baseline HR		0.2388	0.98	(0.95, 1.01)
Baseline NIBP-S		0.2947	0.98	(0.95, 1.02)
Baseline NIBP-D		0.6226	1.01	(0.96, 1.07)
Baseline NIBP-M		0.7391	1.01	(0.97, 1.05)
Baseline RR		0.3754	1.06	(0.93, 1.22)
Baseline $EtCO_2$		0.2021	1.91	(0.71, 5.17)
MDAS		0.3488	1.05	(0.95, 1.14)
Ramsay 5 min	(1 or 2) v 3	0.9023	1.09	(0.27, 4.38)
Ramsay 15 min	(1 or 2) v 3	0.2949	0.32	(0.04, 2.67)
Operating Conditions	(Fair or Poor) V Good	0.3466	0.36	(0.04, 3.01)

5. Discussion

Sedation-related morbidity is primarily associated with drug-induced airway obstruction, aspiration, respiratory depression with hypoventilation and haemodynamic instability [92]. To promote improvements in the quality of patient care, the future pursuit of clinical trials has been recommended to be conducted in a number of areas, including dental conscious sedation using combinations of drugs [93]. Like many aspects of dentistry, the practice of conscious sedation for the operator-sedationist is largely influenced by what they have learnt during training, the available guidelines and personal clinical experience managing patients under sedation. Conventional sedation guidelines are limited by the lack of high-quality evidence but are helpful to guide sedation practice by amalgamating various legislation and guidelines, expert opinion, clinical trials and systematic reviews. The limitations of extrapolating the existing clinical evidence to the practice of conscious sedation in dentistry is restricted by the intricacies of practice specific to oral surgery, which include good accessibility for administering local anaesthetic for effective pain management rather than relying on systemic analgesia; not routinely administering supplemental oxygen which may disguise hypoventilation and defining hypoxaemia at a lower threshold as an early warning sign for ambulatory dental care.

Along with the limited database of evidence, compelling anecdotal reports spanning decades of practice have supported a reputation of safe sedation practice in dentistry. However the prescription of sedative medications with the potential to debilitate a patient's sensorium and potentially jeopardize respiratory function should deter any attitude of complacency regarding safety. Imperatively, the inherent risks associated with combining an opioid with a benzodiazepine require an attentive sedationist to prevent adverse events with vigilant monitoring. Reporting of morbidity and mortality associated with conscious sedation is scant, however it is not considered to be zero. The database of ASA claims identifies respiratory depression due to absolute or relative overdose of sedation agents to be responsible for 21% of claims relating to monitored anesthesia care and over half were deemed to be preventable with better monitoring [94].

A total of 96 patients were recruited to participate in the study and 94 datasets were included in the statistical analysis. At the initial consultation a small minority of patients were excluded due to regular

cannabis use and two patients declined to participate in the study due to concerns for developing an opioid dependency from the one-off dose. No patient raised concerns regarding the potential for respiratory depression. Some were initially referred for sedation but declined this treatment modality in favour of local anaesthetic only once the expectations of sedation were clarified, given that anaesthesia would be effectively achieved by lignocaine injections rather than sedative drugs which were employed to achieve anxiolysis. This highlights the difficulties some patients perceive in deciphering the differences between analgesia and anesthesia. It is important for clinicians to be cognizant of this confusion to ensure the right level of intervention is targeted, whilst educating patients on realistic expectations of their sedation experience. A thorough pre-assessment in collaboration with the departmental RGN helped to ensure appropriate patient selection. During the pre-assessment phase, three patients did not meet our suitability criteria for conscious sedation in the oral surgery department due to increased BMI > 35 kg/m^2 and were referred for sedation with anaesthetic monitoring.

Prior to the 'COVID-19' pandemic, our department occupied sole use of an outpatient theater for DGA which was efficiently operated by a dedicated team of nurses and anesthetists. Like many other dental services, the waiting list for DGA was already over populated owing to a cultural propensity for patient demand-driven general anaesthetic [67]. March 2020 saw the repurposing of our outpatient theatre facility for COVID patients and all elective DGA activity effectively stopped for at least five months. By the end of 2020, CUDSH reclaimed a proportion of its DGA operating capacity in a new facility but now competing with other elective surgical specialties and the demand for this service continues to accrue. A review of patient records was performed to determine if any cases could be appropriately transferred to the conscious sedation list. For those where the surgical task was appropriate in the outpatient department under sedation, patients were contacted by telephone to determine if treatment was still required or had been completed elsewhere. The option of conscious sedation relative to general anaesthetic was discussed. Patients were invited to discuss this further in clinic and the majority welcomed the more accessible option offered by sedation and avoidance of a general anaesthetic, coupled with a more attractive waiting time. A minority remained adamant that their anxiety needs could only be satisfied by receiving treatment under DGA, illustrating the difficulty we face in contending with the cultural demand for DGA and shifting the balance in favour of clinical need.

This issue was highlighted at our departmental clinical governance meeting where clinicians were encouraged to reflect on a tendency for over reliance on DGA. The COVID-19 pandemic may serve to be the turning point in utilizing our sedation service to greater effect [95] and we must be cognizant of the restricted access we now face. This review highlighted many advantages of reserving our DGA for the greatest clinical need and promoting the conscious sedation service, facilitating easier and more timely access to treatment for anxious patients, reducing dental health inequalities and a greater cost benefit ratio to both the patient and the Oral Surgery service in CUDSH. Clinicians have been reminded to carefully ascertain the medical and dental history, explore the nature of a reported dental anxiety and curtail the inclination to be overly amenable to patient demands for DGA [96].

5.1 Primary Objective: Incidence of hypoxaemia

The primary objective of this study was to determine the incidence of hypoxaemia experienced by patients undergoing intravenous fentanyl and midazolam to achieve conscious sedation during oral surgery procedures. As far as we are aware, this is the first study to primarily investigate the incidence of hypoxaemia with intravenous fentanyl and midazolam without the routine use of supplemental oxygen in the oral surgery outpatient environment.

Of the 94 patients included in the analysis, 50 (53%) developed arterial oxygen desaturations to 94% or less. Of the 50 patients that experienced 'any' hypoxaemia, 49 experienced mild hypoxaemia first, some of whom went on to experience moderate or severe hypoxaemia, and 1 patient experienced moderate hypoxaemia only. A further 29 (31%) patients continued to desaturate into moderate hypoxaemia (SpO_2 90-92%), with severe hypoxaemia (SpO_2 <90%) occurring in 19 (20%) patients. As SpO_2 of 94% was an early warning sign to begin verbally stimulating the patient, without this intervention the incidence may have been higher.

Respiratory events were commonly encountered in our study, sometimes frequently within the same course of treatment with the most common respiratory event being hypoxaemia, although apnoea was not an outcome measure of the study. No further adverse events were encountered as a result of desaturating arterial oxygen levels, which were all transient in nature. All participants remained responsive to verbal or light tactile stimulation to improve ventilatory effort, a minority of 6 (5%) patients requiring support from supplemental oxygen. The lowest arterial oxygen saturations recorded by pulse oximetry ranged from 73 – 98%, with the lowest average oxygen desaturation calculated at 92.45%.

Two female patients developed desaturations beneath 80% during courses of sedation delivered by both specialists. The lowest SpO_2 observed was a desaturation to 73%, occurring in a 39-year-old, non-smoker with a BMI of 33.6. She had a high level of anxiety (MDAS score 19/25) and was undergoing a simple forcep dental extraction. Following 50 µg of fentanyl, midazolam was titrated incrementally at a rate of 1mg/min to a total of 5mg. Her oxygen saturations were consistently maintained at 100%

over the period of induction to end point, with the lowest desaturation being subsequently observed in the pre-operative period, 5 minutes after the sedation end point had been achieved. Three minutes prior to the pulse oximeter detecting a desaturation to 73%, the patient had two episodes of apnoea which lasted 25 seconds and 45 seconds respectively, the surgical drapes had not yet been placed so the sedation team could observe very shallow chest rise and fall reflecting the reduced tidal volumes. Supplemental oxygen was delivered at 3L/min and her saturations were restored to above 90% within 20 seconds and maintained for the duration of the procedure.

The second lowest desaturation was observed at SpO_2 75%, similarly in a 39-year-old female, non-smoker with a BMI of 22.4. Her MDAS score was 8/25 and the surgery involved coronectomy of an impacted mandibular third molar. A total dose of 2mg of midazolam was delivered after which the patient's oxygen saturation slowly began to deteriorate to 79%, two minutes after the second milligram of midazolam, but responded promptly to verbal stimulation to breathe. Within 10 seconds, the oxygen saturations were restored to 96% and the sedation end point was determined to be achieved. Despite the patient remaining responsive to verbal prompts to inhale, she was unable to maintain her saturations consistently, deteriorating again to SpO_2 75%, at which point a decision was taken to administer 5L/min of supplemental oxygen. A 'head-tilt, chin-lift' was also performed to relieve airway obstruction, owing to her chin postured in towards her neck. The supplemental oxygen was removed 6 minutes prior to beginning surgery and the patient comfortably maintained her saturations at 98% independently. No further episodes of hypoxaemia where observed upon surgical stimulation.

In both cases the oxygen desaturations were drastically rapid, observed in the pre-operative period, transient and readily recovered with minimal intervention. Whilst both patients remained responsive to verbal and tactile stimulation to increase their respiratory effort, they were unable to maintain saturations above 94% consistently without verbal or tactile prompts to breathe therefore the sedationist/operator decided to administer supplemental oxygen.

The study was powered on an assumed rate of hypoxaemia at 40%. Combining fentanyl with midazolam resulted in a much higher incidence of hypoxaemia at 53% than previously identified in

Brady's study in 2017 using midazolam alone at 37% (Table 20). This result was also greater than any other study identified in the earlier literature review. Perhaps this reflects the lack of routine delivery of supplemental oxygen in our procedure and continuous data collection, allowing for identification of brief, transient episodes which would be more likely missed by recording observations at intervals.

Table 20: Incidence of hypoxaemia with fentanyl and midazolam V. midazolam alone.

	Mooney et. al 2021		Brady et. al 2017	
	N = 94	%	N = 190	%
Any SpO_2 event	50	53	70	37
Moderate SpO_2 event	29	31	46	24
Severe SpO_2 event	19	20	19	10

Guidelines for procedural sedation in endoscopy recommend delivery of oxygen via nasal cannula throughout the procedure [27]. Barriga et al. evaluated the benefit of single versus multi-drug sedation for endoscopy and observed no episodes of hypoxaemia in their study population [84]. Oxygen was delivered via nasal cannula at a rate of 2L/min and it was found that neither patients receiving midazolam alone or in combination with fentanyl desaturated to less than 95%. Concurrent administration of oxygen can disguise the onset of hypoxaemia and delay the detection of reduced ventilatory competency [45]. Monitoring with a pulse oximeter in the presence of inspired oxygen should be interpreted cautiously owing to the artificial increase of arterial oxygen saturations. Whilst Brady et al. failed to show the benefit of capnography monitoring to prevent the occurrence of hypoxaemia in patients receiving single drug midazolam breathing room air, there may be a role for monitoring $EtCO_2$ routinely when multi-drug combinations are employed, due to a greater propensity to suppress central respiratory drive. Current guidelines from the IACSD and SDCEP do not currently recommend the use of additional capnography monitoring for dental sedation, but acknowledge that

additional capnography monitoring may be required for ASA III & IV patients, who are usually not sedated in outpatient facilities.

Our investigation adopted a low threshold for hypoxaemia at $SpO_2 \leq 94\%$ creating an early warning sign for hypoxaemia. A threshold of $SpO_2 <90\%$ is often considered to be the point at which respiratory stimulation would be initiated in primary care oral surgery practice and is quoted in much of the conscious sedation literature. For the purposes of this research, the reasons for maintaining the definition of hypoxaemia at a low threshold of $SpO_2 \leq 94\%$ were two-fold. Firstly, to maintain homogeneity with previous sedation research employing single drug midazolam for oral surgery procedures enabling direct comparisons to be made [46]. Secondly, although both specialists involved in delivering sedation were experienced and had received training in advanced sedation techniques, this was the first time that multi-drug sedation was performed in our dental hospital without cover from anaesthetic colleagues. The 'Dental Council Education and Training Committee' approved this research investigating the incidence of hypoxaemia with opioid and benzodiazepine sedation for developing the evidence base, permitting a divergence from the current guidelines in Ireland. Hence safety procedures were paramount in this study protocol which was reassuringly reinforced by utilizing an early warning sign for hypoxaemia.

The mild to moderate point on the sedation continuum was successfully and consistently targeted by the oral surgeons involved in this study with 82-87% of patients rated as RSS score 3 at five and fifteen minutes from end point respectively. Importantly as per the definition of conscious sedation, patients retained the ability to purposefully respond to commands, including the two patients who developed the deepest levels of hypoxaemia as discussed earlier. Various degrees of respiratory suppression were observed into the 'mild', 'moderate' and severe' categories, however only one patient presented a clinical problem, where the greatest airway intervention executed was 'head-tilt, chin lift'. This supports the suggestion by Garip that despite respiratory depression occurring frequently with combinations of remifentanil and midazolam, this may not be of clinical concern as desaturations were mostly reversed by asking patients to take deep breaths [47].

Prevention and correction of hypoxaemia is required to prevent a patient developing an oxygen deficit, a risk that is considered to be a precursor of adverse events such as cardiac ischaemia. Uncorrected respiratory depression is a potentially life-threatening complication[97] and benzodiazepines can cause profound respiratory depression which is not physiologically compensated[98]. Previous studies have shown an association with hypoxaemia and myocardial ischaemia, with ST-segment depression and tachycardia [99] in people with and without a history of cardiovascular disease[100]. A death was reported in 2002 under conscious sedation in New South Wales attributed to irreversible cerebral hypoxia following a cardiac arrest. This aetiology was determined to be related to a number of episodes where the depth of hypoxaemia continually deepened .

A true operator-sedationist model was not consistently employed as the research investigator observing the monitors identified each episode of hypoxaemia and stimulated the patient's respiratory effort. Therefore the potential incidence of hypoxaemia in the clinical setting is difficult to determine owing to the interventional stimulus early within the plateau of the oxyhaemoglobin dissociation curve, along with the additional 'protective factor' of the research investigator. In Milgrom's study, a respiratory event was defined as apnoea with no respiratory activity for 30 seconds as detected by capnography, but suggested that perhaps even this measure was too conservative because whilst apnoea occurred, it was quickly terminated by an alert anaesthetist reminding the patient to breathe [52]. The benefits of avoiding hypoxaemia by prompt identification and management are indispensable to preventing ensuing complications during conscious sedation.

5.2 Secondary Objective: Timing of hypoxaemia

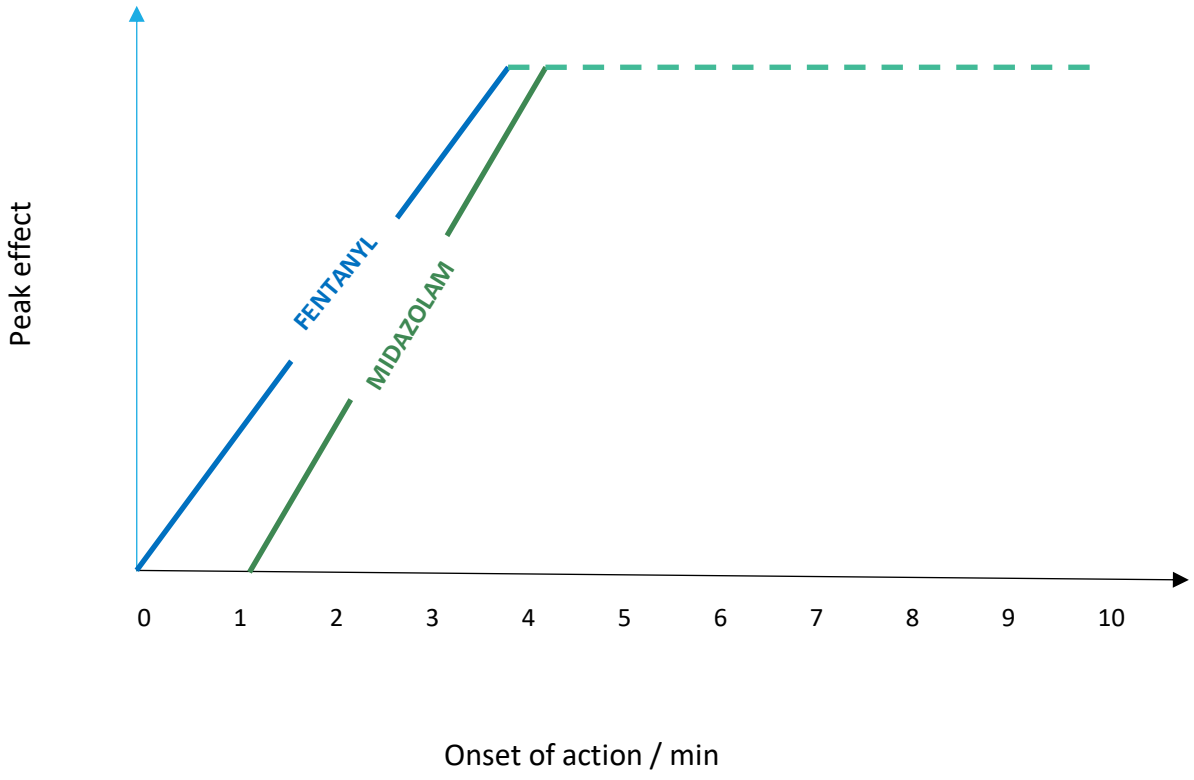
The time to onset of the first hypoxaemic episode was recorded from the point of initial 50mg dose of fentanyl, rather than from the time of sedation end point as determined by the sedationist. This allowed our study to capture any hypoxaemia during the induction phase which could potentially arise due to the synergism between midazolam titrated to effect after the initial dose of intravenous fentanyl. The earliest occurrence of $SpO_2 \leq 94\%$ developed at 42 seconds, which was before the first milligram of midazolam was administered. Overall 90% of hypoxaemic episodes occurred within 13.6 minutes.

To consider the onset of hypoxaemia in relation to "stages of procedure", the vast majority of hypoxaemic episodes occurred between the induction and pre-operative phase and rarely in the intra-operative period once surgical stimulation began. Initiation of surgical stimulus greatly reduced the occurrence of hypoxaemic events with only 12% of episodes occurring during the intra-operative period until the end of monitoring. This finding replicates the observations in Milgrom's study where apnoeic episodes were rarely recorded once local anaesthetic was administered and the surgery began [58].

Fentanyl has a rapid onset of action within 1-2 minutes, reaching peak effect between 3 – 5 minutes, similar to midazolam, reaching peak effect within 3-4 minutes of administration. Midazolam has a linear pharmacokinetic profile over 0.05 – 0.4mg/kg which allows for the predictable titration of dosage to patient response [101]. This contributes to the safety profile of midazolam, whereby incremental dosing to effect allows the sedationist to control the attenuation of the patient responsiveness whilst maintaining protective reflexes [19]. The onset of action of midazolam is more rapid when combined with an opioid (1.5 minutes). The pharmacokinetics of these drugs are represented in our clinical findings, when the greatest synergistic activity should be observed within the first 10 minutes, consistent with the mean onset of hypoxaemia at 8 minutes in our study population (Figure 14).

The information yielded in our results informs dental sedationists when to exert greatest vigilance for the potential occurrence of a hypoxaemic event, specifically in the pre-operative period where two thirds of events were observed in this study. The reality of the clinical environment during this period can see the diversion of the operator-sedationist's attention, such as donning personal protective equipment, reviewing pre-operative radiographs and ensuring all instruments are present for the surgery. Good organization and preparation in advance will prevent distraction from monitoring the sedated patient's respiratory activity particularly in this period where there is increased likelihood of a hypoxaemic event, enabling prompt recognition to reverse the desaturation and prevent an escalation of interventions to manage developing complications. Consideration may be given to delaying placement of surgical drapes until the time coincident with beginning of surgery to enable uninhibited visualization of rate and depth of breathing with chest rise and fall.

Figure 14: Diagrammatic representation of fentanyl and midazolam time to peak effect.



5.3 Secondary Objective: Risk factors for hypoxaemia

Defining risk factors for hypoxaemia could beneficially enhance pre-assessment protocols and intra-operative sedation monitoring to reduce the likelihood of hypoxaemic episodes. In return, this could inform education and training for dental sedationists and improve patient outcomes. Respiratory depression is a significant precursor of morbidity in conscious sedation, thus hypoxaemia is a valuable surrogate measure for adverse events in the outpatient oral surgery department. We assessed for multiple risk factors to identify potential associations with hypoxaemia including:

- Patient characteristics: Age, sex, BMI, smoker & MDAS score
- Sedatives: Dose of midazolam to end point, time from first midazolam dose to end point & intra-operative midazolam
- Specialist 1 V Specialist 2
- Vital signs: Changes from baseline averages of SpO_2, heart rate, blood pressure, respiratory rate & end-tidal CO_2
- Sedation scores: RSS score at 5minutes and 15 minutes & operating conditions

Age

Multivariate logistical regression identified a statistically signification association between increasing age for moderate and severe hypoxaemia. The risk of moderate and severe hypoxaemia increased by 7% & 8% respectively for each added year of age. Qadeer identified a statistically significant relationship between increasing age and hypoxaemia, with patients over the age of 60 years being four times more likely to develop hypoxaemia than the under 60 age group (OR4.1, 95% CI 1.3 – 13.0, p= 0.02) [102]. Several other studies have also identified age to be related to hypoxaemia [48, 103-105].

Theories postulated for the association between age and hypoxaemia have been described to include a reduction in body fat stores, resulting in a greater bioavailability of biologically active opioids and benzodiazepines due to reduced lipid accumulation. The increased sensitivity of elderly populations to sedatives has been widely reported in population-based studies [106]. Therefore, to mitigate the risk

of adverse events, increased awareness and reducing exposure to potentially harmful drug combinations should be exercised [103]. Other physiological mechanisms associated with the aging process including reduced ventilation/perfusion ratio and reduction in hepatic metabolism due to decreased perfusion, protein binding and polypharmacy may have a role to play [102].

Sex

No significant difference was identified between the onset of hypoxaemia and sex. However, when assessing severe hypoxaemia, females displayed an increased odds ratio being 70% more likely than males to develop a hypoxaemic episode but this result failed to achieve statistical significance. In contrast, using single drug midazolam Brady et. al found males were 143.8% (p = 0.325, 95% CI 1.077-5.519) more likely to experience 'any' hypoxaemia than females.

BMI

The risk of BMI and the onset of hypoxaemia has been poorly defined in previous studies which have reported body weight to weakly correlate with hypoxaemia, [107-109] impeded by the diverse populations studied and hindered by vague definitions of both hypoxaemia and BMI. Our study population was represented by a good dispersion of BMI values (mean 25.8, SD 4.2). For each unit of increasing BMI, there was a 7% increase in hypoxaemia however this did not achieve the 5% significance level (p = 0.2209). In contrast to Brady et al.'s study with single-drug midazolam, increasing BMI was found to have a significant association with the risk of hypoxaemia, where patients with a greater BMI were more likely to desaturate ≤ 94% by 18% (95% CI 1.065 – 1.307, p= .0.0015).

Champaneri et al. [110] retrospectively reviewed the pre-operative assessment of 200 patients and the outcomes of IV midazolam and inhalation sedation. Of the obese patients (BMI > 30 kg/m^2), 8% desaturated to SpO_2 <90% lasting a few seconds, successfully managed with simple airway procedures and was not statistically significant ($\chi^2[4] = 9.386$, p=0.052). The authors observed that the levels for desaturation in patients with BMI > 25 kg/m^2 and > 30 kg/m^2 were comparable to other groups and found no significant difference between sedation outcomes. Furthermore, in Qadeer's study[102], increasing BMI failed to achieve significance for hypoxaemia, with every 5 unit increase in BMI

increasing the risk of hypoxaemia by 60%. (p = 0.079). However the authors did report a significant correlation between the frequency of hypoxaemic episodes and BMI (rho 0.26, 95% CI 0.04 – 0.48, p = 0.02), with and without supplemental oxygen. This finding may help better define the relationship between body weight and hypoxaemia, suggesting a link of mechanical obstruction between body weight and the airway, with obstruction a potential basis for increased incidence of hypoxaemia.

Saiso et al. [50] calculated the difference between patients who experience sedation-related complications and those who did not for multiple clinical variables. The only parameter to show a significant difference for sedation-related complications was found in obese patients (≥ 30 kg/m^2) undergoing intravenous fentanyl and midazolam sedation ($P < 0.05$). This result related to three obese patients who experienced arterial oxygen desaturation to 95% following the initial administration of midazolam and fentanyl. The average BMI in Saiso's population was lower than our study (22.8 ± 4.4 kg/m^2) of which 8 (7%) patients were categorised as obese and so external validation of these results to our study is limited. The relationship with obesity is consistent with Qadeer's study, univariate analysis identified an increased frequency of hypoxaemic events between patients categorised as obese rather than non-obese patients, 71% vs. 46%, respectively (p = 0.08) [102].

The body mass index is a routinely recorded measure in the pre-assessment for sedation procedure, providing the operator-sedationist with a judgement on cannulation difficulties and airway assessment with increased fat accumulation around the neck [111]. The escalating obesity epidemic poses a considerable challenge that health care practitioners will have to risk assess and manage. Of the potential subjects to be recruited to this study, increased BMI (≥ 35 kg/m^2) was the major excluding factor encountered to prohibit participation. The overall health risk of obesity cannot adequately be defined by BMI due to variation of fat distribution. An individual with excess weight around the abdomen may pose less risk of airway obstruction in the supine position compared to another who carries increase proportion of adipose around the airway tissues. NICE updated their guidelines to include the measurement of waist circumference in addition to BMI to improve the objectivity of risk posed by obesity [112]. BMI is not the only predictor of oxygen desaturation, opioids and benzodiazepines can cause respiratory depression regardless of weight. Additional assessments to BMI should be considered as adjuncts in risk assessment for outpatient sedative procedures, such as the STOP-BANG questionnaire (Figure 15). This consists of eight questions assessing the risk of

obstructive sleep apnoea which divulge pertinent pre-operative risk factors for risk of airway obstruction [113].

1. Snoring Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	Yes / No
2. Tired Do you often feel tired, fatigued or sleepy during the day?	Yes / No
3. Observed Has anyone observed you stop breathing during your sleep?	Yes / No
4. Pressure Are you now being or have you been treated for high blood pressure?	Yes / No
5. Body mass index >35kg/m^2?	Yes / No
6. Age >50 years?	Yes / No
7. Neck circumference >40cm?	Yes / No
8. Gender Male?	Yes / No

Figure 15: The STOP-BANG questionnaire. A score of 3 indicates a risk of obstructive sleep apnoea whereas a score <3 indicates low risk [110].

This study supports the existing literature that BMI is ineffectual as a surrogate measure of airway obstruction and consequentially a risk for hypoxaemia. It may be beneficial for future research to include more pertinent measures of airway assessment such as a ratio of neck circumference to weight and height or sleep apnoea scores for an association with risk of airway obstruction and hypoxaemia.

ASA Classification

The American Association of Anaesthesiologists Physical Status (ASA PS) classification system was introduced by Saklad in 1941, with the intention of creating a classification system for statistical analysis and to stratify disease [114]. The purpose of ASA is not to assess the operative risk, as it is devoid of incorporating the effects of the surgical insult on the pre-existing patient co-morbidities, "no attempt should be made to prognosticate the effect of a surgical procedure upon a patient of a given physical state' [115]. Conscious sedation guidelines specify that an ASA category is assigned to each patient who is pre-assessed for conscious sedation . It may be useful in categorising the

ambulatory status of the patients as ASA I or II, however the inherent subjectivity between anaesthetics and medical/dental specialties in assigning categories has previously been shown to vary considerably among professionals who use the classification [116].

Although many authors have chronicled that ASA classification is a significant risk factor for hypoxaemia, the confounding effects within the diverse populations of ASA I & II patients limits accurate description of the specific nature of risks posed by ASA I & II patients. Qadeer et al. [102] acknowledged this problem and aimed to determine the significant risk factors for hypoxaemia (SpO_2 < 90%) in ASA I & II patients undergoing endoscopy procedures with opioids and benzodiazepines. Hypoxaemia was defined at a higher threshold (SpO_2 < 90%) and the reported incidence was similar to our study occurring in 40/79 (51%) of the patients at least once[102]. Variables contributing to ASA classification which were associated with an increased onset of hypoxaemia included age and meperidine dose, with BMI increasing the frequency of hypoxaemic episodes. We did not include ASA in our analysis as it strongly corelates with smoking status (ASA II), which was included in the multi-variate logistic regression analysis instead.

The reports of association between ASA and sedation complication rates are variable. Inverso [117] investigated a difference in complications between two levels of sedation, moderate versus deep sedation/general anaesthetic. The study population included 29,548 participants with an average age of 17.3 ± 1.7 years, with variable sedatives administered including propofol and ketamine. Multivariate logistic regression analysis identified an association with ASA level and a 72% increase in adverse events (OR = 1.72, 95% CI 1.24 – 2.38, P = 0.001). In contrast, Senel [118] assessed the complication rate of sedation with co-morbidities finding that 22.2% of medically compromised subjects developed complications, whereas 44.3% of this cohort did not develop any (OR 2.78, 95% CI 0.57 – 13.58 p = 0.207).

Dose of midazolam

One of the benefits often chronicled with multi-drug sedation is the reduced doses of each analgesic/sedative required to achieve sufficient anxiolysis to enable successful treatment. The average dose of midazolam required to achieve sedation end point in combination with fentanyl was

5mg with a range of 2-9 mg (SD 1.4). This represented a 28% dose reduction when compared to Brady et al.'s single drug study, where the average midazolam dose to achieve end point was 6.94mg, with a much wider range between 3-20mg (SD 2. 31) (Table 21).

Table 21: Comparing midazolam doses delivered during multi-drug and single drug intravenous sedation.

	Fentanyl & Midazolam (2020)		**Midazolam (2017)**	
Total midazolam dosage / mg	**N**	**%**	**N**	**%**
2	3	3	-	-
3	7	7	3	2
4	27	29	19	10
5	26	28	26	14
6	16	17	39	21
7	12	13	40	21
8	1	1	30	16
9	2	2	14	7
10	-	-	11	6
11	-	-	2	1
12	-	-	1	1
13	-	-	2	1
15	-	-	1	1
Total ALL Patients / mg	**94**		**190**	
Mean Dosage / mg	**5**		**6.94**	
Standard Deviation / mg	**1.4**		**2.31**	

Moore et al. used bivariate analysis to identify three pre-sedation factors to be related to the titrated dose of midazolam. These included preceding dose of an opioid ($p<0.0001$), baseline heart rate ($p<0.001$) and systolic blood pressure ($p<0.05$) [48].

This result is consistent with the pharmacokinetics describing the synergism between opioids and benzodiazepines and is also in line with results from Milgrom[119], Lobb[51] and Moore[120]. Milgrom reported a significantly lower average dose of midazolam for initial titration when fentanyl was given first compared to midazolam alone (< 0.001). Lobb reported that the total midazolam dose was 2.43mg less when fentanyl was delivered first, also observing that patient recollection of the procedure was significantly greater. The amnesic effect of midazolam is particular advantageous with oral surgery procedures as patients often cite the desire to not be able to remember the surgical event. Fentanyl has no amnesic properties; therefore the reduced midazolam dose may be counterproductive to the favourable amnesic effects. This may potentially negatively impact the quality of patient satisfaction, however Moore found that this outcome was not significantly affected. Further qualitative studies would be required to assess the difference in amnesic effect gained by adding fentanyl to midazolam. Previous studies have shown no substantial benefits when fentanyl has been added to diazepam and methohexital [121].

Arterial pulse oximetry and End tidal Carbon dioxide

Both SpO_2 and $EtCO_2$ yielded significant associations as risk factors for hypoxaemia. The risk of hypoxaemia increased by 190% with each 1% reduction in SpO_2 from baseline and for each 1kPa reduction in $EtCO_2$ from baseline, the risk of hypoxaemia increased by 192%. Whereas lower $EtCO_2$ arising from increased ventilation can protect against hypoxaemia, it is also plausible that lower $EtCO_2$ reflecting lower CO_2 arterial partial pressure ($PaCO_2$) could serve to destabilise breathing, especially in sedated patients, which in turn may give rise to hypoxaemia. As $PaCO_2$ falls, a sedated patient moves closer to their apnoeic threshold, and hypocapnia-induced hypoventilation or overt apnoea would result in oxygen desaturation.

An experimental study without surgical stimulation was carried out by Bailey et al. [3] to better define the blunting effect of fentanyl and midazolam on ventilatory responses. The authors reported that low doses of midazolam alone (0.05mg/kg) did not result in hypoxaemia or apnoea in healthy, young adults. Fentanyl alone resulted in hypoxaemia in 6/12 subjects but no apnoea. When midazolam was added to fentanyl, the combination resulted in hypoxaemia in 11/12 and apnoea in 6/12 subjects. The authors hypothesised from these results that depression of hypoxic ventilatory drive occurs sooner and to a greater extent that the ventilatory responses to hypercarbia with both these drugs.

Blood pressure

Cardiovascular parameters remained stable throughout induction to recovery in all of our study participants. A statistically significant result was identified in the multi-variate logistical regression analysis regarding mean blood pressure. For each 1mmHg higher than baseline mean blood pressure, the risk of hypoxaemia increased by 6%.

Fentanyl is known to have hypotensive effects due to its potential to reduce systemic vascular resistance, whilst benzodiazepines are relatively free from cardiovascular effects at clinical doses. It is not uncommon for patients to present with increased systolic blood pressure readings on arrival to the sedation suite, potentiated by anxiety. A reduction in heart rate and blood pressure were observed with small doses of fentanyl and midazolam sufficient to achieve anxiolysis, but at no point in our study was there a significant alteration from baseline requiring an intervention.

Side effects

There were no episodes of nausea or vomiting among the participants within our study population. Postoperative nausea and vomiting are usually related to the dose, pain severity, and types of anesthesia and surgery. No other medications were administered such as anti-emetics or steroids. Senel et al. reported nausea and vomiting to be the most common complication, occurring at a rate of 22.2% with midazolam and fentanyl for oral and maxillofacial surgeries [118]. Minor paradoxical reactions were observed where it was noted that a minority of younger female patients tended to become tearful during induction and pre-operative periods.

5.4 Implications of research

Implications for future research

This is the first investigation to report the incidence of hypoxaemia occurring with intravenous fentanyl and midazolam specific to the oral surgery environment. Whilst previous figures have been reported in the medical literature, the validity to oral surgery is limited as procedural sedationists tend to employ opioids for their analgesic effect, beyond the desirable synergism with midazolam. This results in a tendency for greater doses of fentanyl to be delivered which is potentially hazardous to cardiorespiratory stability. Analgesic doses used in procedural sedation are not replicated in the dental environment where the surgical site is more amenable to effective local anaesthetic.

Whilst the study methodology was designed with the intention of an operator-sedationist model, in reality this was not feasible owing to the institution's responsibility for training specialist oral surgeons who became primarily involved in performing many of the surgical procedures after the sedationist achieved the sedation end point, along with the protective factor of the research investigator identifying each episode of hypoxaemia. The level of vigilance attainable with the operator-sedationist model remains a controversial aspect of sedation monitoring, with anaesthetic colleagues recommending monitoring responsibility with a qualified practitioner not involved in performing the surgery. The Canadian Anesthesiologists Society practice guidelines state that "it is unacceptable for a single physician to administer an anaesthetic, including deep procedural sedation, and simultaneously perform a diagnostic or therapeutic procedure, except for procedures done with only infiltration of local anaesthetic and/or minimal sedation" [122]. Our research does not provide reliable data on the incidence of hypoxaemia observed with a sole clinician being responsible for both monitoring and performing the surgery. Therefore, we recommend further research to validate the ability of a dental sedationist administering parenteral sedatives and analgesics to safely monitor the patient and simultaneously perform the operation.

Based on expert opinion, the SDCEP guidelines advise to "only use an advanced technique if the clinical needs of the patient are not suited to sedation using a standard technique". This presents an opportunity for further qualitative research to determine the advantages regarding the sedation

experience from both the patient and surgeon's perspective. Measures that would be worth investigating include patient and operator satisfaction with the standard compared to advanced techniques as well as determining if there is a difference in the quality of anxiolysis intra-operatively and amnesia post-operatively experienced by the patient.

Conscious sedation guidelines specific to dental sedation have so far refrained from advising the routine use of capnography monitoring for basic techniques, with conclusions from existing research failing to show a significant reduction in the occurrence of oxygen desaturation with single drug IV sedation. International guidelines take a different perspective, such as the Canadian Anesthesiologists Society[122] and American society of Anesthesiologists [123] who recommend carbon dioxide monitoring during conscious sedation. The Australian and New Zealand College of Anesthetists [124] recommend supplemental oxygen to be administered to all patients undergoing procedural sedation for all diagnostic and therapeutic procedures to prevent hypoxaemia. The routine use of supplemental oxygen is not currently recommended with our current standard, whilst its use is acknowledged for the prevention of hypoxaemia, it can also mask hypoventilation with ensuing consequences. With the greater incidence of hypoxemia occurring with fentanyl and midazolam, investigating the use of supplemental oxygen to prevent hypoxaemia with capnography monitoring to detect hypoventilation may have a role in reducing the incidence of hypoxaemia during multi-drug sedation in the dental outpatient setting. To answer this question, a randomized controlled trial with carbon dioxide monitoring comparing groups who do and do not receive supplemental oxygen throughout the procedure would be useful. The operator would be blinded to this intervention and respiratory stimulus would be prompted based on capnography monitoring for all participants and the observed difference of hypoxaemia rate between both groups determined.

Implications for conscious sedation in practice

Our data shows that the greatest number of hypoxaemic events are most likely to occur in the pre-operative period and we can infer this to be considered as a high-risk time during sedation. This has implications for sedation in the clinical environment where sedationists need to exert greater vigilance for monitoring arterial oxygen saturations in the pre-operative period.

A robust foundation of education and training is fundamental to the safe and effective delivery of conscious sedation. The 2015 IACSD guideline was applauded for providing a syllabus for sedation training including a comprehensive list of learning outcomes for advanced sedation techniques. Prior to this, a course based on the Independent Expert Group on Training and Standards for Sedation in Dentistry (IEGTSSD) training syllabus was introduced for internal staff at Guy's and St Tomas' NHS Foundation Trust. The course consisted of self-directed study modules and didactic training[125]. A significant barrier to implementing an advanced conscious sedation service with competent sedationists is access to validated training courses in advanced techniques and attaining appropriate supervision to complete the minimum clinical experience of twenty cases with monitored practice recommended to achieve competence. A number of guidelines [27, 122] have highlighted the need for advancing clinical standards and effectiveness in sedation with the implementation of a multi-disciplinary committee, representative of the various stakeholders in sedation, such as anaesthetics, medical specialties involved in procedural sedation and dental conscious sedation. The members of the 'Sedation team' would ideally be involved in the delivery of education and practical expertise, contributing to improvement in the quality of patient care, with the benefit of increasing the availability and mobility of sedation services as well as promoting ongoing education and skill acquisition of team members. A collaboration between specialties involved in sedation across an institution, led by an anaesthetics would help with accreditation of advanced sedation providers within the service, where patients of the greatest need can be more safely and predictably managed.

A substance categorised as a 'controlled drug' is subject to control under the Misuse of Drugs Act 1977 to 2016, with different restrictions controlling the supply of each schedule of controlled drug. The Health Products Regulatory Authority (HPRA) lists the authorised controlled drug products and should be referenced for accurate and current information regarding classification. As Fentanyl is categorised as a Schedule 2 drug, it is a statutory requirement to adhere to the legislation 'Misuse of Drugs

Regulations' (2017). Cork University Dental School & Hospital obliged by Regulation 14 of the Misuse of Drugs Regulations 2017, placing an appropriate requisition order with pharmacy and following safe prescribing and dispensing of fentanyl and maintaining a controlled drug register. An unfortunate case of non-compliance was reported by the media in 2020, outlining the failure of an experienced Specialist Oral Surgeon in Northern Ireland who unwittingly did not maintain a controlled drug register for the use of fentanyl in his practice [126]. This reputable specialist, esteemed among colleagues for providing advanced sedation for special care patients, breached legislation with failure in recording the use of three hundred and forty ampoules of fentanyl. The General Dental Council did not impose any restrictions as no adverse events occurred and many patients were successfully treated. Unfortunately, this deficiency of clinical governance led to a 12-month conditional charge as a result of failing to maintain a chronological sequence of fentanyl entries in a controlled drug register. This case resonated with many dental professionals involved in sedation, whereby a clinician who could not possibly be contested for upholding the Hippocratic Oath, instead had their professionalism challenged due to an oversight of controlled drug management. This case highlights the importance of dental sedationists to be aware of their lawful obligations concomitant with the use of fentanyl in sedation practice, as failure to comply may compromise their professional registration and potentially face criminal charges.

There is no intention to replace the use of standard sedation techniques with the routine use of advanced sedation techniques, as IV midazolam continues to be well tolerated by patients and maintains comfortable safety margins for sedationists in dental practice. Failed single drug sedation should not be considered as the only absolute indication for IV fentanyl and midazolam as this may be a disservice to patients with significant anxiety traits. If we consider the only pathway to advanced sedation to be as a result of failed sedation, this may unethically expose patients to distressing episodes and further deteriorate compliance with dental health. We recommend for the advanced sedation techniques to be used appropriately and proportionately. However, choosing the sedation technique for each patient is wholly subjective, based on sedationist experience, patient's dental anxiety history, medical history and tolerance of benzodiazepines. Ideally the development of a validated assessment tool to incorporate objective measures would be useful in avoiding subjecting anxious and phobic patients to failed sedation before progressing to advanced techniques. Incorporation of medical, dental, drug and social history combined with validated anxiety tools would usefully inform the prescription of which pharmacological sedative technique may be more likely to

meet each patient's needs and facilitate successful treatment. At present there is no guidance indicating one technique over another, other than potentially trial and error which may be to the detriment of patient acceptance of an advanced sedation technique rather than DGA.

Too often in secondary care we receive referral letters for oral surgery procedures under general anaesthetic from primary care practitioners. It is difficult to determine whether this is a result of dental practitioners succumbing to patient demands at the coalface, or a lack of awareness of the significant number of anxious patients who are successfully managed under conscious sedation. Treatment planning and behavioural management discussions with patients who are attending consultation under the premise of a 'promised' general anaesthetic, compounded by their anxiety can create a significant challenge for our department. Attempting to adjust a patient's perspective to acceptance of treatment under conscious sedation, which we know may more appropriately target the right level of intervention for their needs, may be a heroic endeavour. To address these shortcomings, providing our referrers with information on our sedation services such as an indication of current waiting times for conscious sedation versus general anaesthetic and audit results of patients successfully managed under our sedation service may improve insight for referrers. Further to this, adjusting our referral proforma to include a check box prompting referrers to consider which treatment modality is required, such as local anaesthetic with or without conscious sedation or general anaesthetic could be a useful 'aide-memoir'. Within our department, introduction of a care-pathway following consultation were the practitioner is required to formally record the indication of the selected treatment modality may further help reduce the default to general anaesthetic, reducing the burden on an over-subscribed waiting list.

Quality assurance of our conscious sedation practice in Cork University Dental School and Hospital is indispensable regardless of which sedation techniques are employed. We continue to advocate regular audit of our sedation service including documenting any adverse events or significant critical incidents with appropriate systematic review and recommendations for improvement where indicated.

5.5 Strengths & Limitations

The primary and secondary objectives of this study are clearly defined at the outset and have not been previously addressed by this method in the existing evidence base. This is the first study to measure the incidence of hypoxaemia and the study design most fitting to answer this question is a prospective, observational study measuring the onset of hypoxaemia during a course of surgical treatment under intravenous sedation. The study is limited by including only one study arm where all participants received fentanyl and midazolam with no additional arm for comparison of hypoxaemia incidence with midazolam alone. Therefore, there was no random allocation or stratification for baseline characteristics among participants. Our results discussed the baseline characteristics of the study population, constituting reasonably balanced proportions of sex, wide spread of BMI and age ranges. A significantly greater number of patients, time and clinical resources would have been required to include an additional study arm of midazolam only sedation to facilitate the comparison. On balance of the research gains this may have offered, along with the clinical constraints this would have imposed on the oral surgery department, the additional group of study participants was not justified to yield significant advantage to this research project. The incidence of hypoxaemia with single drug midazolam as reported in a previous study was accepted as a suitable for comparison for discussion.

The study methodology demonstrates good internal and external validity measuring the incidence of hypoxaemia as a proportion of those who developed oxygen saturations less than or equal to 94% versus those that did not. We are confident that these results can be generalised to patients likely to receive sedation in Ireland as Cork Dental School and Hospital encompasses a wide referral base. Strict inclusion and exclusion criteria were mapped to existing guidelines to ensure appropriate patient selection for sedation with the defined ages, BMI and ASA categories being included in the study. Inferences can be made from our study to patients who meet suitable criteria for sedation as our study protocol aligns with the existing IACSD and SDCEP guidelines. Additionally, potential effects on the primary outcome were limited by consideration of cofounding factors which could bias results which were included in the exclusion criteria, such as current use of opioids which could potentiate the synergetic action with midazolam and chronic use of CNS depressants which could lead to a tolerance of reasonable sedative doses. Taking all this into consideration, the results can only be generalised to ASA I & II patients and cannot be extrapolated to those with significant systemic disease.

The method for administering sedation followed the procedure typically performed in the dental outpatient settings, whereby supplemental oxygen is not given routinely to mask hypoventilation and local anaesthetic effectively manages pain control without reliance of further parenteral analgesic administration. The study was performed in the context of ambulatory procedures rather than simulation and included a wide range of surgeries which are commonly performed in both primary and secondary care oral surgery services. Conscious sedation is commonly performed in oral surgery for a number of treatments, therefore we did not limit this to one specific type such as third molar surgery in order to enhance the validity. Consequentially, we have gleaned from our results that the incidence of hypoxaemia greatly reduces once surgical stimulation begins. By not stratifying the procedures, we may have potentially introduced performance bias as the surgical stimulation for a simple forcep extraction in a severely anxious patient is not equal to that of an autogenous bone graft using a reciprocating saw. Attrition bias was minimal with only two data sets lost during transfer. Data cleaning allowed any aberrant readings as a result of artefacts such as a dislodged pulse oximeter or ipsilateral placement of a pulse oximeter on the arm of blood pressure cuff to be accounted for prior to statistical analysis. We did not perform an analysis on how much data was not recorded as a result of artefacts, but this was considered by the statistician to be minimal.

Data were recorded at five second intervals, which was as close as we could achieve for continuous measurement of arterial oxygen saturation. This allowed for fluctuations in arterial oxygen saturation to be closely followed and limited the potential for detection bias; if data had been collected at greater time intervals then the incidence of hypoxaemia may have been lower. Likewise, if it was not for the research investigator continually prompting respiratory stimulus upon saturations of 94% then the incidence of moderate and severe hypoxaemia may have been greater. The presence of a research investigator provided a level of vigilance that would not have been possible with an operator-sedationist alone and therefore further research is required to determine the safety of combined drug sedation in this type of clinical setting.

The sedationists were not blinded to the monitor for the initial induction period when sedation was delivered, therefore the potential for performance bias was present. In some instances further increments of midazolam were withheld based on the pulse oximeter reading rather than clinical

evaluation of the patient's signs of sedation. Two specialist oral surgeons were involved in the delivery of sedation and no significant difference was determined with the incidence of hypoxaemia between operators, supporting the generalisability of results to oral surgery practice. The operating conditions were graded according to four categories by each specialist immediately on completion of each case. No calibration was performed to standardize the grading of operating conditions between the two specialists. This was not deemed to be necessary as both oral surgeons shared similar experience in both surgery and conscious sedation and have worked together in the same unit for many years.

The clinical end point of hypoxaemia was well-defined and clinically relevant to the practice of conscious sedation allowing for an achievable sample size to be calculated. To investigate end points of greater morbidity such as cardiac or cerebral hypoxia would entail recruitment of an extremely large number of patients out with the scope of a single-centre study and would be more difficult to measure. Hypoxaemia was a categorical, binary outcome categorised on a three-tiered scale to align with previous research, allowing for comparisons with other literature to be made. Conscious sedation literature has been criticised for lacking heterogeneity among definitions and methodology. Our study endpoint definition of hypoxaemia recognises that in clinical practice hypoxaemia is often defined as an SpO_2 < 90% which may be the more valuable outcome for the majority of dental practitioners involved in delivery of conscious sedation.

To avoid a type II error, a power calculation was performed to identify the number of patients required to achieve the minimum clinical difference, determined from previous research which more closely followed our study design. Only one paper was identified to guide the power calculation set at 80% with an assumed rate of hypoxia at 40%. A compromise was made regarding the accepted margin of error for the study at 10% because a smaller margin of error would have required a larger number of participants that was not possible to accommodate in the given time frame for completion of the study.

As the onset of hypoxaemia is a binary dependent variable, multivariable logistic regression analysis was a suitable method for quantifying the impact of numerous independent variables on the outcome. We considered a comprehensive list of independent factors to assess for associations with

hypoxaemia and presented these as odds ratio along with displaying the confidence intervals allowing transparency of the result's precision. Cautious conclusions should be drawn from our secondary objective as the sample size of the study was not powered to assess for associations between multiple independent variables as risk factors for hypoxaemia. Despite not achieving statistical significance, we considered the clinical significance between female sex and severe hypoxaemia which showed a relatively large odds ratio. No attempt was made to test multiple hypotheses other than the clearly defined objectives set out at the beginning of the study, avoiding inflation of a type I error. Clinical interpretation of the results was given equal weight to the statistics whereby although a high incidence of hypoxaemia was observed, we know that the majority were transient, reversed with verbal or tactile stimulation and no adverse events occurred as a result.

6. Conclusion

This observational study has been useful to identify the incidence of hypoxaemia observed in patients undergoing intravenous sedation with fentanyl and midazolam during oral surgery outpatient procedures. Within the limitations of this study, we can make the following conclusions:

The data support that hypoxaemic events occur frequently in patients who are sedated with intravenous fentanyl and midazolam sedation during oral surgery procedures. The observed incidence of 'any' hypoxaemic event was 53%, with 32% continuing to desaturate to 'moderate' hypoxaemia and 20% of study participants deteriorating to 'severe' hypoxaemia.

Two-thirds of all hypoxaemic episodes were observed to occur within the pre-operative period following achievement of the sedation end point. Overall, 90% of hypoxaemic episodes developed within the first 13.6 minutes from the time of fentanyl administration. Dental sedationists should be most vigilant for a hypoxaemic event between the time of sedation end point and before the surgical procedure begins.

Each episode of hypoxaemia was transient and successfully reversed in the majority of patients with verbal and mild tactile stimulation without any further complications. Escalation of airway intervention was rarely required as only one patient required a 'head-tilt, chin-lift' to relieve upper airway obstruction.

Identifying risk factors can help to improve safety outcomes of conscious sedation by informing clinicians of the patient characteristics which are more likely to be associated with an unfavourable hypoxaemic event. The risk of experiencing 'any' hypoxaemic event was associated with:

- Dose of midazolam to end point: Reduced risk of hypoxaemia with each additional milligram of IV midazolam.
- Baseline SpO_2: Increased risk of hypoxaemia for each 1% reduction in SpO_2 from the baseline value.
- Mean blood pressure: Increased risk of hypoxaemia for every 1mmHg increase in mean blood pressure from the baseline value.
- $EtCO_2$: Increased risk of hypoxaemia for every 1kPa reduction in $EtCO_2$ from the baseline value.

Our study identified age to be a significant risk factor for developing 'moderate' hypoxaemia and 'severe' hypoxaemia:

- 'Moderate' hypoxaemia: For each additional year of age the risk increased by 7%.
- 'Severe' hypoxaemia: For each additional year of age the risk increased by 8%.

The sedationist should exert heightened vigilance among the patient cohort of advancing age and practice dosing restraint. This may be achieved by using smaller increments of titrated sedatives, or increasing the time interval between titrations to allow for a longer observation period to clinically determine when the patient has achieved the sedation end point.

There was no associated risk for hypoxaemia with sex, smoking, pre-operative MDAS score, vital sign measures such as heart rate or respiratory rate, sedation scores and operating conditions.

Future research is required to determine the suitability of an individual dental clinician acting as an operator-sedationist to identify hypoxaemic episodes during fentanyl and midazolam sedation for oral surgery procedures. The use of capnography monitoring and supplemental oxygen for dental patients undergoing conscious sedation by combining an opioid and benzodiazepine warrants further investigation to determine the potential effectiveness in reducing the incidence of hypoxaemia as observed in this study.

These results enhance the dental evidence base and support dental sedationists undertaking intravenous fentanyl and midazolam sedation. The increased likelihood of hypoxaemia, particularly in the pre-operative period requires prompt recognition to instigate early intervention to correct oxygen saturations by stimulating patient's respiratory effort to prevent ensuing complications.

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Appendix 1 – Ethical Approval

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (q) 03/12/19

Date: 3rd December 2019

Dr Paul Brady
Consultant in Dental Sedation
Oral Surgery Department
University Dental School and Hospital
Wilton
Cork

Study Title: Investigating the incidence and magnitude of hypoxaemia with intravenous fentanyl and midazolam sedation for oral surgery procedures in adult patients.

Approval is granted to carry out the above study at:

Cork University Dental School and Hospital and Cork University Hospital.

The following documents have been approved:

Document	Approved	Version	Date
Application Form	Yes		
CV for Chief Investigator	Yes		
Proof of Insurance	UCC		
Study Protocol	Yes		
Participant Information Leaflet and consent form	Yes		
Study Questionnaire	Yes		

We note that the co-investigator(s) involved in this project will be:

Name	Occupation
Eimear Mooney	Postgraduate Doctorate in Clinical Dental Surgery
Professor Ken O'Halloran	Professor of Physiology, UCC
Dr Gabriella Iohom	Consultant Anaesthetist.

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Appendix 2 – Patient information and consent

Patient information

Study title: An investigation into the incidence of hypoxaemia during intravenous sedation with fentanyl and midazolam for oral surgery procedures

Chief investigator: Eimear Mooney

Contact number: 0214901100

You are invited to participate in an optional research study investigating advanced methods of conscious sedation. The oral surgery department in Cork Dental School is investigating the use of multi-drug sedation to develop the sedation service that can be offered to our patients. You can decide whether or not you would like to participate in the study by reading this information sheet which outlines the details of the study, procedure involved, risks, benefits and alternatives. The chief investigator will discuss the project with you and answer any questions that you may have. You will be given some time to consider your options and it you would like to participate then proceed to complete the consent form at the end of the information section.

What is the advanced sedation technique and why is this study being done.?

Sedation is commonly used during oral surgery procedures which can often provoke fear and anxiety, creating a deterrent for some patients. Effective management of your pain and anxiety is an important consideration for your oral surgeon in order to improve your tolerance. Conscious sedation is beneficial to reduce your anxiety, allowing you to be more relaxed during treatment, whilst still being awake and able to communicate with your dental team. The sedation delivered in dental practice normally involves a single intravenous

benzodiazepine drug called midazolam. This method is a well-established technique, commonly performed to help facilitates oral surgery procedures and has an excellent safety profile. You will still require an injection of local anaesthetic in your mouth to numb the area during treatment.

This study aims to use an additional opioid drug called fentanyl which incorporates properties for pain relief and improving the level of sedation. Together, these drugs are given slowly to meet your needs, according to your level of anxiety. The benefit of adding fentanyl is that it can help overcome the uncomfortable sensation of having injections and help reduce any pain experienced during the treatment. Together these drugs can be combined to improve your comfort throughout and improve the sedative effect as you undergo your dental procedure.

This advanced technique using both fentanyl and midazolam has been used in other dental hospitals internationally, but is yet to be established in Ireland for conscious sedation. One of the risks of this procedure is that your effort of breathing can be reduced causing reduced oxygen levels in your blood. The research will allow us to measure the occurrence of reduced work of breathing, the number of times that this occurs, the time at which it is most likely to occur after giving the sedative drugs and by how much breathing can be affected. We will also me monitoring other clinical signs to assess if there are any changes, for example to heart rate or blood pressure. Other reported side effects of these drug combinations include nausea.

This is prevented by titrating the drugs slowly to your response and we will also be using additional breathing monitors, giving us information about how well your lungs are being ventilated. This monitor will measure the amount of carbon dioxide in your expired breath as well as a pulse oximeter probe on your finger to measure the amount of oxygen in your blood. These will create alarms to let your oral surgeon know if your breathing is beginning to reduce, allowing us to take measures to increase your breathing effort, usually by instructing you verbally to take deep breaths or applying extra oxygen via nasal prongs. In case of emergency, the effects of both of these drugs can be reversed.

What will happen if you decide to participate?

If you decide to have intravenous sedation, it is likely that you will have two appointments, whether or not you decide to participate in the study. At the first appointment, you will undergo our normal assessment procedures to ensure you are suitable to receive intravenous sedation in our oral surgery department. At this appointment we will confirm the dental treatment you require, discuss your medical history and any

medications that are prescribed by your doctor. Measurements will be recorded of your height and weight as well as your blood pressure, heart rate and oxygen concentration in your blood.

If you are assessed to be suitable then we will give you instructions for before and after your dental procedure with sedation. On the day of treatment, we will check your medical history and measurements again. A small cannula will be placed into a vein in your arm or back of your hand, allowing the sedative drugs to be given. You will have a probe placed on your finger, blood pressure cuff on your arm, ECG heart monitors in your chest and a disposable nasal cannula allowing is to monitor you throughout the sedation. These monitors will be kept on until the treatment has been completed and you are fit to be sent home with your escort which should be between one to two hours.

Measurements that will be taken during the procedure include:

1. Arterial blood oxygen saturation: Measured continuously with the pulse oximeter finger probe.
2. Expired carbon dioxide level: Measured continuously using the disposable oro-nasal cannula
3. Respiratory rate: Measured continuously using the disposable oro-nasal cannula
4. Heat rate: Measured continuously with the pulse oximeter finger probe.
5. Blood pressure: Taken every 15 minutes or more frequently (depending on result) via the blood pressure cuff
6. Level of sedation: Assessed by the oral surgeon during treatment.

The measurements recorded will be stored in a computer system and will be labelled by a code so that any information will not directly identify you. The measurements will be stored for three years when the study should be completed. No other tests will be performed other than those described to you here.

If it is observed that your breathing effort is reducing, we will instruct you to take deeper breaths. This is often enough to correct your effort to breathe. In some instances, we may give you additional oxygen and rarely may use airway adjuncts to help maintain your airway. In the rare, serious event that we are concerned that your breathing is not recovering with these interventions, we will use two drugs to directly reverse the effects of the fentanyl and midazolam which are called naloxone and flumazenil, respectively.

What are the side effects or risks you can expect from fentanyl and midazolam intravenous sedation?

The oral surgeon and dental nurse will monitor you closely during the sedation with help from the appropriate monitoring equipment. Risks of the sedative medications include:

A reduction of oxygen in your blood circulation as your effort to breathe starts to reduce. You will be instructed to take a deep breath which is usually enough to correct this.

Bruising at the site of the cannula. The cannula is inserted using a small needle which is then removed, leaving the cannula in. No more needles are required to deliver the sedation drugs once the cannula is in place.

There is a small risk of becoming more deeply sedated than intended when both fentanyl and midazolam are used. You are closely monitored whilst the medications are given slowly to avoid this. In adverse events, the effects of the medications can be immediately reversed.

You may forget some parts of the dental treatment from the point at which the sedative drugs are given. Some people have no memory at all of the procedure. This can also be an advantage in particular when people are very anxious about their treatment.

After the sedation you may feel unsteady on your feet for a few hours and a=your ability to think clearly and make judgments can be affected for twenty-four hours.

Very rare side effects include:

Nausea and vomiting

Allergic reaction

Chest wall rigidity is a potentially serious reaction to administration of fentanyl which is quite rare, occurring after intravenous injection of fentanyl affecting the muscles in your chest and the muscle used for breathing.

What benefits can you expect from the fentanyl and midazolam sedation technique?

Sedation will help you to feel drowsy and relaxed.

You will remain conscious throughout the procedure however you may have some memory loss of the procedure after you have been given the sedation, with some people having no memory of the procedure at all.

The addition of fentanyl has the potential to reduce the amount of pain that you will feel. You will also be given an injection of local anaesthetic to numb the area. Fentanyl can help the injection feel less uncomfortable

What are your options?

It is your decision whether or not you would like to participate in this study. You may decide to:

1. Participate in the study using fentanyl and midazolam for intravenous sedation during your oral surgery procedure (along with local anaesthetic)
2. You can decide to participate, however if you decide to change your mind at the time of treatment we can proceed with only midazolam for sedation, or without sedation
3. Not participate

What will happen if you decide not to participate?

If you decide not to participate in the study you have a number of options, if you intend to proceed with your oral surgery procedure:

1. Undergo the standard, single drug technique involving only intravenous midazolam to help you to relax you as you undergo the oral surgery procedure.
2. Proceed with the oral surgery procedure using local anaesthetic alone, without any sedation.

What if you change your mind?

If you decide to participate but change your mind on the day of your surgery, we can still provide you with intravenous sedation using midazolam only which is the standard technique practiced in our department.

If you participate in the research study but chose to stop participating thereafter, we will destroy any data which has been collected and not use any of your data for analysis.

AGREEMENT TO CONSENT

The research project and the treatment procedures associated with it have been fully explained to me. I have had the opportunity to ask questions concerning all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at University Dental School and Hospital, Cork. I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the Chief Investigator listed above. I understand that the study has been approved by the Cork Research Ethics Committee of the Cork Teaching Hospitals (CREC) and if I have further queries concerning my rights in connection with the research, I can contact CREC at Lancaster Hall, 6 Little Hanover Street, Cork, 021 4901901.

Please circle yes or no for the following statements:

I have read and understand the study: yes / no

I agree to participate in this research: yes / no

I grant permission for the data collected to be used in this research only: yes / no

I understand that my anonymised data will be stored at Cork Dental School for seven years:

Chief Investigator Signature: _____

Signature of Study Participant: _____

Witness Signature (if applicable): _____

Legal Representative Signature (if applicable) _____

Date: _____

Appendix 3 – Modified Dental Anxiety Score

CAN YOU TELL US HOW ANXIOUS YOU GET, IF AT ALL, WITH YOUR DENTAL VISIT?

PLEASE INDICATE BY INSERTING 'X' IN THE APPROPRIATE BOX

1. **If you went to your Dentist for TREATMENT TOMORROW, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

2. **If you were sitting in the WAITING ROOM (waiting for treatment), how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

3. **If you were about to have a TOOTH DRILLED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

4. **If you were about to have your TEETH SCALED AND POLISHED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

5. **If you were about to have a LOCAL ANAESTHETIC INJECTION in your gum, above an upper back tooth, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

Instructions for scoring **(remove this section below before copying for use with patients)**

The Modified Dental Anxiety Scale. Each item scored as follows:

Not anxious	=	1
Slightly anxious	=	2
Fairly anxious	=	3
Very anxious	=	4
Extremely anxious	=	5

Total score is a sum of all five items, range 5 to 25: Cut off is 19 or above which indicates a highly dentally anxious patient, possibly dentally phobic

Appendix 4 – Intra-operative data collection proforma

Date	Operator-sedationist	Indication	Procedure

Study ID

Patient details

Age	Sex	BMI	ASA	MDAS	Smoker

Medications

50µg Fentanyl (min)	Midazolam Endpoint time (min)	Midazolam end point dose (mg)	Time to end point (min)	Intra-op midazolam (mg)

Timing

Baseline monitoring (5min)	Monitoring time (40 min from end point)	Operation start – end time

Ramsay Sedation Scale Score:

Level	Description
1	Anxious, agitated, restless
2	Cooperative, oriented, tranquil, accepts mechanical ventilation
3	Responds to commands only
4	Brisk response to light glabellar tap or loud noise
5	Sluggish response to light glabellar tap or loud noise
6	No response to light glabellar tap or loud noise

5 min from operation start: ____

15 min from operation start: _____

Episodes of hypoxia: **Yes/No**

Severity 93-94%/ 90-92%/ <90%	Lowest SpO2	Baseline /Induction/ Intra-op/Post-op	Time(s)	Intervention	Supplemental O2

Assessment of operating conditions:

1. Good: Patient fully co-operative with optimum degree of sedation	2. Fair: Minimal interference from patient due to over/under sedation	3. Poor: Operating difficult due to over/under sedation	4. Impossible

Comments

Appendix 5 - Conference abstracts

International Association of Dental Research: Irish Division meeting

February 2021

TITLE: Incidence of Hypoxaemia with Intravenous Fentanyl and Midazolam Sedation for Oral Surgery Procedures.

PRESENTER: Eimear Mooney

AUTHORS (FIRST NAME, LAST NAME): Eimear Mooney[1], Michael Cronin[2], Ken O'Halloran[3], Paul Brady[1]

INSTITUTIONS (ALL): 1. Cork University Dental School and Hospital, University College Cork, Cork, Ireland.
2. School of Mathematical Sciences, University College Cork, Cork, Ireland.
3. Dept. of Physiology, University College Cork, Cork, Ireland.

ABSTRACT BODY:

Objectives: Respiratory depression and airway compromise may result in serious consequences if untreated during conscious sedation. The primary aim was to investigate the incidence of hypoxaemia (SpO_2 ≤94%) in ASAI&II patients undergoing intravenous sedation with fentanyl and midazolam. The secondary aims included determination of the onset time of hypoxaemic events and significant risk factors for hypoxaemia.

Methods: This prospective observational study required 92 patients to achieve a power of 80% at the 5% significance level. A total of 96 patients, (57 female, aged 16-65) met the inclusion criteria and consented to participation. The operator/sedationist delivered a standard dose of 50µg of fentanyl followed by titrated midazolam, at a rate no greater than 1mg/min. Oxygen saturations were monitored via pulse oximetry and supplemental oxygen was not given routinely, unless indicated. Verbal or tactile stimulation was performed to encourage respiratory effort when SpO_2 ≤94%. Monitoring continued for forty minutes from the time of sedation end point. Data was exported from the 'BeneVision N12 Mindray' monitor to Microsoft Excel. Statistical analyses (logistical regression) were performed in SAS® (Version 9.4).

Results: All participants successfully completed treatment and 94 patients were included in the analysis. 50 (53%) individuals developed hypoxaemia, with 19 (20%) proceeding to severe hypoxaemia (SpO_2<90%). Following administration of fentanyl, 90% of hypoxaemic events occurred within 13.6 minutes; the majority (66%) were observed during the pre-operative period. The risk of hypoxaemia increased for each 1% reduction in SpO_2 and 1kPa reduction in $EtCO_2$ from baseline by 190% and 192%, respectively. The risk of moderate and severe hypoxaemia increased by 7% (p=0.0003) & 8% (p = 0.0002) respectively, for each added year of age.

Conclusions: This study presents information on the incidence of hypoxaemia for multidrug sedation in ASAI&II patients in an outpatient oral surgery department. Whilst the hypoxaemia incidence was found to be 53%, all patients remained responsive to respiratory stimulation, consistent with the definition of conscious sedation. Heightened vigilance for desaturation is required for reductions in SpO_2 and $EtCO_2$ from baseline, 13.6 minutes following fentanyl administration and with advancing age.

Title: Risk Factors for Hypoxaemia in Single and Multi-drug Intravenous Sedation for Oral Surgery Procedures

Presenter: Eimear Mooney

Authors (First name, Last name): Eimear Mooney[1], Michael Cronin[2], Ken O'Halloran[3], Paul Brady[1]

Institutions (ALL): 1. Cork University Dental School and Hospital, University College Cork, Cork, Ireland.
2. School of Mathematical Sciences, University College Cork, Cork, Ireland.
3. Dept. of Physiology, University College Cork, Cork, Ireland.

Objectives: Respiratory depression is a significant precursor of morbidity in conscious sedation, thus hypoxaemia is a surrogate measure for adverse events in the outpatient department. The primary objective is to compare risk factors associated with hypoxaemia (SpO2 ≤ 94%) in ASA I & II patients receiving midazolam with or without fentanyl IV sedation for oral surgery procedures.

Methods: The onset of hypoxaemia was recorded prospectively during oral surgery procedures in 284 ASA I & II adults (F=186) between 16-65 years. Titrated doses of midazolam were administered to Group A and B, with an initial 50µg fentanyl bolus given to the latter. Supplemental oxygen was administered if arterial oxygen saturations failed to remain above 94%, following verbal and tactile stimulation. Multivariate logistic regression analyses were performed for multiple clinical variables in each group to identify associated risk factors.

Results: Hypoxaemia occurred in 70 /190(37%) of group A and 50/94(53%) of group B participants. Increasing age was significantly associated with group A (OR = 11.394) and group B (OR=1.08). Males were 143.8% (p=0.0325) more likely to develop hypoxaemia in group A, however sex was not statistically significant in group B, despite an increased odds ratio (OR=1.7) for SpO_2 <90% in females (p= 0.3295). With increasing BMI, the odds of hypoxaemia increased by 18% in group A only.

Patients with higher baseline $EtCO_2$ were 12.2% less likely to have a hypoxaemic event in group A($p = 0.0039$) and for each 1kPa reduction in $EtCO_2$ from baseline, the risk of hypoxaemia in group B increased by 192%($p = 0.0203$).

Conclusions: Defining risk factors for hypoxaemia may improve safety outcomes for ambulatory conscious sedation procedures. We have identified clinical variables which may be considered as risk factors for the onset of hypoxaemia; including age, sex, BMI & $EtCO_2$ for both standard and advanced techniques.