Research Article

Safety of Conscious Sedation/Analgesia for Dentistry; A Comparison of Midazolam/Fentanyl Vs Promazine/Meperidine

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Abstract

The anesthesia charts of adult patients undergoing dental surgery lasting >1 h (sinus lift, multiple implants, multiple wisdom teeth extractions) were retrospectively analyzed comparing meperidine/promazine (MEPPROM, 93 cases, 2018-20) to midazolam/fentanyl (MIDFENT, 415 cases, 2011-2020). Patients signed an informed consent, completed a health questionnaire; afer diazepam premedication and full monitoring sedation started with midazolam 1-2 mg: the group MEPPROM received the mixture according to weight, the group MIDFENT received additional midazolam and fentanyl 25-50 microgr. Midazolam for sedation or fentanyl for analgesia was allowed in both groups on demand, aiming at Ramsay score 2-3. Dental anesthesia (articaine or mepivacaine + epinephrine) followed, repeated as needed. The study variables were collected every 5 minutes on specially designed sheets:oxygen desaturation (<90%), brady/tachycardia (<50, >120 bpm), hyper/hypotension (>180, <90 mmHg systolic or >30% difference versus basal), sleep (Ramsay score 4), hypercapnia (etCO2> 40 mmg), nausea, vasovagal reactions, arrhythmias.

Age (59), weight (KG 70), height (cm 167). ASA class (1-3), sex were equally distributed between the 2 groups; surgery was longer in the MEPPROM group (148 min vs 118) (averages). Hypertension incidence was similar, but 40 MIDFENT patients received clonidine vs 1 in the MEPPROM. Frequence (%) of hypotension (20 vs 2), tachycardia (15 vs 1), bradycardia (11 vs 4) were always greater in the group MEPPROM. Incidence of desaturation, hypercapnia, excessive sedation were similar. Side effects did not differ:nausea (2 MEPPROM, 4 MIDFENT but with frequent use of haloperidol), vasovagal syndromes (2

MEPPROM, 5 MIDFENT). All patients were discharged within 1 hr after surgery. Under careful titration MEPPROM offer clinical conditions similar to the established MIDFENT routine; however haemodynamic disturbances are more frequent and call for expert vigilance and continuous monitoring of vital signs.

1. Introduction

In march 2018 the American Society of Anesthesiologists (ASA) published a new practice guidelines on moderate procedural sedation and analgesia [1]. The very comprehensive report endorsed by the scientific societies more involved in the field of sedation and analgesia (ASA, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, Society of Interventional Radiology) reported recommendations which cover all aspects of moderate sedation and analgesia according to its precise definition: "moderate sedation/analgesia (pre- viously called conscious sedation), is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway when spontaneous ventilation is adequate. Cardiovascular function is usually maintained. …".

Special attention was given to the effectiveness and safety of various methods and interventions that might be used during sedation/analgesia, with emphasis to patient evaluation, preparation, monitoring. Medications quoted included almost all drugs of anesthesiological interest:midazolam, ketamine, remifentanil, fentanyl, dexmedetomidine, etomidate either alone or in combination. The findings summarized in the text followed the criteria of better evidence, defined as results obtained from randomized controlled trials, scientifically superior to findings obtained from observational studies. Efficacy of a drug technique cannot be evaluated solely from the positive results of a trial: type of surgery is just one aspect to be considered when comparing different techniques, since it seem obvious that anesthetic techniques well suited for endoscopy or orthopedics cannot be equally effective in plastic or dental surgery. Dental surgery, and particularly wisdom teeth surgery, offers a good model against which the efficacy of an anesthetic technque can be tested: but the dental impaction model relies on postsurgical pain generated via the extraction of third molars. The model has been in widespread use for over 50 years, is well characterized, and is frequently used to investigate the pharmaco-dynamic properties of analgesic molecules (onset/offset, time to peak effect, duration of analgesia, dose-response, potency) [2].

However as important as postoperative analgesia could be, the intraoperative challenge is a more complex task, since the choice of drugs or combination thereof has to be evaluated from the point of view of all the variables involved, which considering the perioperative confounders, are so many as to impact heavily on the results. As a consequence comparison of different anesthetic techniques could be investigated considering clinically important variables, like impact on the physiology of the patient, incidence of adverse effects [3], facility of use, costs just to mention some important

points.

In our country (Italy) starting from 2018 has not been possible to buy (even under a regimen of strict surveillance and special prescription forms) intravenous sedatives (midazolam, propofol) and analgesics (fentanyl, alfentanyl) in the public pharmacies; only accredited facilities could obtain these controlled drugs. What's more there has been an acute shortage worldwide of the aforementioned drugs, in part attributable to the enormous consumption of these short acting drugs (midazolam, propofol and fentanyl) administered in large quantities to the great number of very sick Covid 19 patients to be sedated admitted in the ICU's and Intensive therapies. As a consequence many dental offices could not obtain midazolam and fentanyl any more and anesthesiologists working in these premises were obliged to find new drugs that could be legally purchased. Phenothiazines (promazine, chlorpromazine), meperidine and morphine were and are available: as a consequence we decided to administer them to patients undergoing dental treatment and for whom anesthesiological assistance was required. Goal of this paper has been to compare the safety profile of the newly adopted regimen (from 2018) (promazine/meperidine) (MEPPROM) vs the older usual technique midazolam/fentanyl (2011-2020) (MID FENT).

2. Patients and Methods

The study was performed on adult patients scheduled to undergo light/moderate sedation for a variety of office dental procedures (multiple implants, sinus lift, cysts exeresis, multiple wisdom teeth extractions) under local anesthesia. Inclusion criteria were age 18 years or older, American Society of Anesthesiologists physical status I, II, III, surgery lasting at least 60 min. Patients completed a routine lab work up (and a 12 leads ECG if older than 65 years); fasted for 6 hours before surgery.

Premedication was given in the holding room with diazepam 1mg/10 kg BW (5-8 mg, p.os) 20-30 min before their arrival in the operating room. Written informed consent was obtained for all subjects and all completed a written health questionnaire, whenever feasible sent and controlled by email a few days in advance. The day of the operation all patients were evaluated for potential difficult airways with the combination of 6 tests [4].

Standard monitoring included noninvasive blood pressure (NIBP), heart rate (HR), 3 or 5 leads electrocardiography (ECG), SpO_2, $etCO_2$ (sidestream), respiratory rate, temperature. An intravenous cannula (22 or 20 g) was secured in the forearm or hand for administration of fluids (3 ml/hr) and medications. All patients breathed through a nasal cannula (Salter labs ®divided cannula), with O_2 suppplementation when needed (SaO_2 90% or less). Intraoperatively, the patient's level of sedation was assessed using the Ramsay five-level scale [5] maintaining a score between 2-3., i. e, patient calm, cooperative, responding to commands. The patient's recovery of function after surgery was assessed using the Aldrete score, to whom was added ability of walking without aid, dressing, orientation to date, place plus some elementary calculation. Intraoperative and postoperative pain was assessed by means of a visual analogue scale. Perioperative side effects were also recorded; oxygen desaturation(<90%), brady /tachycardia (<50, >120 bpm) hyper/hypotension (>180, <90 mmHg systolic or >30% difference compared with the basal), pain on injection, disruptive movements, vivid dreams, nausea, and vomiting. Patient data were collected every 5 minutes on specially designed sheets. Data were retrieved from the paper archive, transferred on Excel sheet and then analyzed with a statistical software (ACASTAT). MIDFENT patients numbered 415 (2011 to 2020); MEPPROM patients numbered 93 from 2018

to nov 2020. Ethical permission was not required since data were retrieved retrospectively from the anesthesia charts and names of patients were cancelled from the data base; cases lasting less than 60 minutes were not included in the analysis.

2. 1 Study protocol

After arrival in the operating room and after baseline values had been obtained, all patients received midazolam 1-2 mg.; then the group MIDFENT received fentanyl 0.5_0.7 microgr/kg while the group MEPPROM received the mixture of meperidine/promazine (2:1) according to weight(kg): 10/5 mg for BW<50 kg, 15/7.5 mg for BW 51-65, 20/10 mg for BW 66-75, 25/12. 5mg for BW > 76 kg infused within 10 min diluted in 100 ml of normal saline. The cocktail of MEPPROM consists of 100 mg of MEP with 50 mg of PROM, i. e. MEP 1/PROM 0.5 ratio, for instance 1 mg of MEP/0.5 mg of PROM for every ml, since from the practical point of view 1 ampul of MEP (100 mg) and 1 ampul of PROM (50 mg) are injected in a bottle of normal saline (100 ml), from whom 10, 15, 20 or 25 ml are withdrawn to be once again injected in another 100 ml bottle of normal saline to be infused i. v. in 10 minutes. We consider the systematic dosage error derived from the dilution, being in fact 104 ml, to be negligible. Once achieved the desired sedation state (Ramsay score 2-3) patients were given local anesthesia

(LA) with 4% articaine or 2% mepivacaine (both + epinephrine) for alveolar dental block with or without maxillary/mandibular block.

Surgery started after having assessed the effectiveness of the local anesthesia, usually after 5-10 min. Top ups doses of analgesics (mep/promaz mixture 0.5 ml or fent 25 microgr or morf 1-2 mg) were given in the MEPPROM group, while the MIDFENT group received fentanyl: LA was supplemented during the procedure when patients experienced pain (visual analogue scale score> 4). Rescue doses of Midaz 0.5-1 mg boluses and fentanyl 12.5-25 microgr were administered for sedation and analgesia respectively in both groups (Table 1). At the end of surgery, all patients received ketorolac 30 mg and dexamethasone 4 mg intravenously. All patients were discharged home within 1 hour after surgery. Clonidine 45-90 microgr was used for hypertension (defined as >180 systolic or > 95 diastolic); atropine 0.5/0.6 mg for bradycardia defined as HR<50 min. Vasovagal reactions were treated with atropine (0.5 -0.7 mg/) + ephedrine (5-10 mg) + crystalloids(100-200 ml bolus) + supplemental O_2 + adoption of the Trendelemburg position; in case of nausea alone haloperidol was given 0.4/0.5 mg i. v. Hypercapnia was defined as $etCO_2$> 40 mmhg; sleep defined as patients sleeping, but arousable with loud command or pinch (RAmsey 4).

Protocol
Premed: diazepam by mouth 1 mg/10 kg BW
Induction
midaz 1-2 mg+all patients
Group MEPPROM acccording to weight(MEP/PROM 10/5 for BW<50 kg)
MEP PROM 15/7.5 for BW 51-65
MEP PROM 20/10 for BW 66-75
Mep Prom 25/12.5 for BW >76
GROUP MIDAZFENT: fent 0.5-0.7 microgr/kg

Maintenance
MEPROMgroup :mepprom 0.5 ml (Mep 5/promaz 2.5) or morph 1-2 mg or fent 12.5-25 microgr
MIDFENT group; fent 12.5-25 microgr,
both groups: MIdaz 0.5-1 mg for sedation, AL top up in both group

Table 1: Protocol, Induction and Maintenance.

Data collected included the following variables:sex, age, weight(kg), height(cm), ASA class, drugs used with dosages, side effects like hypertension, hypotension, tachycardia, bradycardia, desaturation, hypercapnia, sleep, additional medications and complications. All patients were visited by their dentist within 48 h from surgery and questioned about pain, PONV, local swelling, any other discomfort, general satisfaction.

3. Results

All patients were satisfied with the results of anesthesia and surgery; 3 complained of PONV at home, responsive to oral ondansetron. All would be glad to repeat the same sedative experience, as in fact many did.

3. 1 Statistics

Ordinal continuous data were compared between the two drug groups by means of Student T statistics, while non continuous data incidence of complications BP $\uparrow/\downarrow$, HR $\uparrow/\downarrow$, CO_2 $\uparrow$, and its duration were analyzed with non parametric tests, Cross tabulation Chi square, Mann Whitney, Kruskall Wallis tests. Statistical tests were 2-tailed, with $P < .05$ considered significant. Patient demographics (age, weight, height, sex, ASA) did not differ between the two groups; duration of surgery (min) was longer in the MEPPROM group 148.7 +- 66.8 vs 118. 6+-52, P<0.0001. Patient overall satisfaction with the techniques used was not collected (unfortunately); we based our evaluation from the surgeons opinions, generally reported as very good.

	Meperidine/Promazine	Midazolam/Fentanyl
age(years)	58 ± 16	60 ± 16
weight(kg)	70. 6 ± 14. 5	72. 7 ± 26. 8
height(cm)	167 ± 9	167 ± 9
ASA 1	56. 9%	47.7%
ASA 2	32. 2%	36.6%
ASA 3	10. 7%	14.4 (1. 2% ASA IV)
sex: female	60. 2%	56.6%
male	39. 9%	43.3%
surgery duration(min)	148 ± 66	118 ± 52
Hypertension: NO	81%	72%
YES	19%	28%
Hypotension: NO	78%	97%
YES	20%	2%
Tachycardia: YES	15%	1%

NO	85%	98%
Bradycardia: YES	11%	4%
No	88%	96%
Desaturation : YES	13%	14%
NO	87%	86%
Hypercapnia: YES	24%	38%
NO	70%	56%
n/a	3%	5
Sleep: YES	23%	18%
NO	77%	82%
side effects	5:3 vasovagal, 2 intraop nausea	12:3 exs, 3 resp depression, 2-3(??) vasovagal, 2 nausea intraop, 2 ponv

Table 2: Patient Demographics of Meperidine/Promazine and Midazolam/Fentanyl.

	MEPPROM	MIDFENT	Statistics
hypertension	19%	28%	NS, P<0.32
hypotension	20%	2%	P<0.0001
tachycardia	15%	1%	P<0.0001
bradycardia	11%	4%	P<0.0037
desaturation	13%	14%	NS
hypercapnia	24%	38%	P<0.036
sleep	23%	18%	NS, but P<0.26
maintenance midaz consumption mg	2.31 ± 6.46	2.90 ± 6.34	NS, P 0.31
maintenance fent consumption microgr	8.34 ± 18.4	31.84 ± 37.9	P<0.0001
side effects number	4	12	NS
hypercapnia duration(min)	10. 4	13.2 ± 28	MW: u 15.136, P<0.029; KW H 4.24, P<0.03
other drugs:			
haloperidol 0-4-0.5 mg	0	130	
clonidine: 45-90 microgr	1	40	
side effects	5/93	12/415	Chi sq NS

Table 3: MEPPROM, MIDFENT and Statistics.

4. Discussion

The phenothiazines as a class (promazine, chlorpromazine) disappeared form the anesthesia scene at the end of the 80' substituted by shorter acting sedatives with less side effects, more precise receptor targeting like midazolam and propofol. Phenothiazines use in

anesthesia derived from their potent sedative, antiemetic, antinausea and antihistaminc effects, so that these drugs were generally, combined with meperidine and morphine (Lytic cocktail), either as i. m. preanesthetics or at the induction of anesthesia, especially inhalatory, thanks to their potentiating effects. Today their use is confined to veterinary anesthesia [6] or reserved for psychiatric illness like schizophrenia and severe psychosis [7], often as a mean to obtain a rapid tranquillization in the context of acute agitation, excitement or aggression secondary to a psychiatric disorder [8]. More recently it has been noted a lower incidence of Covid infection in the psychiatric population under chlorpromazine treatment and the role of phenothiazines as chemotherapeutic agents is under investigation [9-10]. Nowadays phenothiazines are still used as general purpose antinausea and antiemetics [11] but their use in psychopharmacolgy is slowly decreasing because the troublesome effects of extrapyramidal motor disturbances and the occurrence of prolonged drowsines and sedation. Since some of theyr effects depend from the blockage of a variety of receptors particularly acetylcholine (muscarinic), histamine (H1), noradrenaline (alfa) and 5HT we believe they could be exploited to success even in the difficult environment of office anesthesia. As a matter of fact 1% of our patients (1/93) got nausea even though many could be considered at high risk [12]. The occurrence in the MIDFENT group was similar but small doses of haloperidol (0.2-0, 4mg) were gived 38% of times in this group only, certainly contributing to the good results (Table 3).

The sparing effect of promazine on respiration was confirmed in this series; no patient exhibited a respiratory depression vs 3 in the MIDFENT group: hypercapnia incidence was lower also (24% vs 38%), with lesser duration of elevated etCO2 (non parametric MW and KW tests) (see Table 3). Incidence of high

blood pressure did not differ between the 2 groups. Incidence of low blood pressure, high and low heart rate were more frequent in the MEPPROM series, most probably as a consequence of the vasodilatatory properties of this association. This effect may be important in the genesis of the episodes of vasovagal reactions noted; reactions occurred intraop in the MEPPROM series and postop in the MIDFENT group. These disturbances call for continuous vigilance from the part of the anesthesiologist and for an immediate reaction in order to prevent more serious consequence. The syncope like effects could be attributed to the trigemino-cardiac reflex [13] but positionings were different (supine vs semisitting, as per surgical convenience); crystalloid infusion could have been different even though rates of infusion were standardized at a median o f 2 ml/hr normal saline in order to reduce the need of the bathroom visits (non too infrequent…) in fact we noted a trend toward more generous allowances in the MEPROM group particulalry at the beginning of the case (data not shown), most probably because of the bias of vasodilatation known to occur with the lytic cocktail. Other variables that add more complexity in the evaluation of the haemodynamic data could be the frequent addiction of small dosages of haloperidol (0.2-0.4mg) and clonidine; haloperidol administered generally in the first minutes of the procedure only in the MIDFENT series (130 injections), with the aim to add a potent antinausea drug to the ongoing medications. These supplementation could have add something to the hypotension side due to the alfalytic properties of the butirophenones group, but these effects seem unlikely at these very low dosages. Worth mentioning the generous supply of clonidine in the MIDFENT group (40 cases): this is probably the cause of the lack of significance of the variable "hypertension" since clonidine has been used only once in the MEPROPM group, where the anesthesiologist

makes good use of the vasodilatatory capabilities of the cocktail in order to maintain a stable haemodynamics helping the smooth progress of the operation, without any significant blood oozing. Moreover clonidine possesses sedative and analgesic properties useful in this context [14]. All in all, the lytic cocktal seems to have more haemodynamic alterations, but the fact that clonidine has been used so frequently in the MIDFENT group casts doubt about the clinical significance of any difference between the two groups.

The most serious side effect was the appearance of sudden episodes of vasovagal reactions;the incidence of this complication has been 1.% (5patients) (Table 3). The occurrence is similar to that encountered in interventionl injection procedures done under xRay guidance (2.6%) [15]; other centers [16] reported lower rates of vasovagal reactions (<1%) in a large series of joint nerve blocks; other series on interventional pain procedures reported a lower incidence (1%) [17]. Vasovagal reactions occur frequently in other environments; for instance the incidence was reported at 5% during femoral arterial sheath removal [18]. The reaction was treated very aggressively as described above in order to minimize the potential sequelae; all subjective symptoms (always reported by the patients as a fainting sensation) and clinical signs disappeared in the course of a few minutes as checked by the speeding up of the measurements of HR, BP and questioning of patients. The difference in side effects were not statistically significant (chi square + Yates correction): it is a statistical non sense trying to analyze them in detail but the results call for more data. Monitoring must cover at least the first 30 minutes following the completion of the procedure since while the vasovagal reactions in the MEPPROM group appeared intraoperatively, 2 over 3 of the vasovagal reactions in the MIDFENT group appeared later, after the patient left the dental chair, during the Cat scan control in the

standing position:that means that supervision must cover the immediate postop also. As a matter of fact the iv cannula is left in situ with the three way stopcok attached and closed until discharge. We defined a very low level of SaO_2 (90%) as a threshold limit for desaturation even though in many studies in the dental literature (and not limited to dentistry) the safety limit has been set at 94% [19], The steepness of the oxyhemoglobin curve indicates a dangerously low level of PaO_2 at 90% saturation, but these episodes were generally short and responded promptly to low flow oxygen (0. 5-1 lt/min), higher flows administered in patients exhibiting a vasovagal reaction.

Many studies show a clear link between use of sedation and risk of hypoxemia [20, 21]; Milgrom and colleagues [22] reported on 207 sedations testing the hypothesis that combined drug therapy (midazolam and fentanyl, or a double-blind placebo) results in significantly poorer safety but no difference in efficacy, compared with the single drug approach. ;in fact the addition of the narcotic resulted in apnea in 63% of cases versus 3% in the midazolam-only group. Interestingly, patients in the combination drug group were 4 times more likely to report an ''excellent sedation'' versus ''good, fair, or poor'' in the single drug group. A study done under the auspices of the, Royal Australian College of Dental Surgeons and the Australian and New Zealand College of Anaesthetists [23] failed to show differences in hypoxemic episodes between patients receiving midazolam and fentanyl or both drugs plus propofol for short periods of more intense stimulation; factors determining desaturation were sex, with males more more likely to experience low-saturation events than females., age, since increasing age was linked to more desaturations events, weight, since the high weight group was nearly twice as likely as the low weight group to experience low-saturation events. From these studies we can assume that the combination of

midazolam and fentanyl is reasonably safe from the point of view of oxygen saturation; our experience with the group MepPROM is similar [Table 3]. We assumed as potency equivalent that 10 mg of meperidine compare with 10 micrograms of fentanyl or 1 mg of morphine [24]; as a consequence the MIDFENT group received more analgesia than the MEPPROM group as shown in the maintenance period also (31.8 microgr vs 8.3): but we are aware that differences in potency estimates exist in the literature [25-27].

Since promazine is a more potent sedative than midazolam the MEPPROM group offer advantages as far as the consumption of fentanyl is concerned ;in fact MEPPROM does not require more midazolam during the procedure, The pharmacokinetics of midazolam and promazine are very different and this is the reason why we used the lytic cocktail for longer procedures, as shown in the table above. The original mixture by the inventor of the Lytic cocktail [28, 29] included promazine, chlorpromazine and meperidine, but this combination was regarded as too potent, since we cannot forget that a prerequisite of the office sedation is the fast discharge of the patient. From this point of view the experience has been succesful so far, since all patients have been sent home accompanied by an adult escort within 1 hr following the completion of surgery. We also believe that any residual sedation due to the long lasting metabolites of diazepam and promazine could be an advantage since keeps the patient calm and relaxed at home and prevents actually their engagement in any physical or mental activity that could cause sudden surge of blood pressure, contributory to hemorrhages and oedema. We recall the case of one patient, a strong hypertensive man under anti hypertensive therapy, who suffered a transient ischemic attack while cutting the branches of a tree in his garden the day after a prolonged and complicated implant surgery of 4 hours: he fell off the ladder, picking up a nasty arm fracture: the CAT scan revealed that the accident was caused by an acute ischemic/hemorrhagic brain event, fortunately small. Of course this man did not follow the written recommendations we gave him. From these experience we believe that for the most invasive dental surgery the lytic cocktail + midazolam and small rescue doses of fentanyl represent a valid technique for maintaining a safe range of oxygen saturation even in the absence of oxygen supplementation and contributes to a smooth intraoperative course with modest side effects., with the added advantage of sparing midazolam and fentanyl and avoiding propofol.

5. Conclusion

careful titration of sedatives and analgesics is of paramount importance for the succes of office base surgery. The drugs used should possess intrinsic safety, be devoid of dangerous side effects and offer favourable pharmacokinetic/pharmacodynamic profiles well suited to the non operating room practice. Even although MEP and PROM are far from ideal drugs to be considered in this setting, they may still deserve a place under well controlled conditions. The priming with these drugs allowed surgery to proceed safely with a minimal dosage of the precious MIDAZ and FENT, these last drugs used more as rescue rather than corner stones.

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