J Oral Med Oral Surg 2024;30:34
https://doi.org/10.1051/mbcb/2024032

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Systematic Review

Management of acute oral pain using methoxyflurane: a systematic review

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(Received: 10 July 2024, accepted: 4 November 2024)

Keywords: Analgesic / methoxyflurane / oral pain

Abstract – Aims: Acute oral pain is a leading cause of presentations to emergency care. Methoxyflurane (MTXF) is a halogen gas with significant analgesic properties at low doses. MTXF administration was reported for dental pain with controversial results. The safety and simplicity of using a recently approved hand-held inhaler represent encouraging evidence for its application for dental pain. Thus, a systematic review was conducted with the following objectives: to determine the efficacy of MTXF in the management of acute dental pain, and to highlight the most effective procedure. **Methods:** This literature review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) methodology. **Results:** Overall, 62 publications were identified, from which 5 articles were selected for this work. The overall quality of the included studies was low with a fairly high risk of bias. In the vast majority of studies, the level of pain experienced by patients using MTXF was low to very low. However, in some circumstances, injection of an additional local anesthetic was required for complete pain relief. The occurrence of adverse effects was low. **Conclusion:** All of the publications highlighted the promising properties of inhaled MTXF at low doses for acute dental pain relief.

Introduction

Acute pain, and oral pain in particular, is a leading cause of presentations to emergency care [1,2]. Currently, the most up-to-date pain management strategy comprises pharmacological interventions including acetaminophen, nonsteroidal anti-inflammatory drugs, and non-opioid and opioid analgesics [3,4]. But despite significant advances, both in the effectiveness of analgesics and in pain relief procedures, pain management and assessment are still inadequate in many cases, and particularly for oral pain management [5]. Moreover, unsuccessful management of acute pain may lead to an increased risk of chronic pain development [2].

Among the alternative procedures to pharmacological oral or parenteral administration of analgesics for rapid pain relief is the use of halogenated volatile agents. Methoxyflurane (MTXF) is an old and well-known volatile anesthetic used for general anesthesia starting from the early 1960s [6–8]. It is absorbed by the lungs and metabolized in the liver *via* CYP450 enzymes. Approximately 60% of absorbed methoxyflurane is excreted by urine in the form of organic fluorinated derivative, fluoride and oxalic acid. The remainder is expired unchanged or as carbon dioxide. Because of renal impairment, its use as an inhalational anesthetic agent was withdrawn in the 1970s [9,10].

The profound analgesic properties of MTXF at a low dose were recognized early on [11,12]. For a short-term relief of acute trauma pain, low-dose MTXF delivered through a hand-held inhaler was first used by the Australian emergency services in the early 1970s [13,14]. More than 5 million doses of inhaled MTXF have been used for trauma patients with no significant adverse events reported [15,16]. All of the recent studies evaluating the efficacy of 3-mL MTXF administered *via* a hand-held inhaler reported mild to moderate related adverse events, which were brief and self-limiting, mostly nausea and dizziness [17–21]. This MTXF administration procedure provided high-quality and well-tolerated analgesia for a variety of outpatient procedures such as colonoscopy [22], bone marrow biopsy [23], prostate biopsy [24], burn dressings [25], minor surgical procedures [26], or in obstetric practice [27].

In oral domain, dental practice in particular, the safety and simplicity of MTXF administration were documented in early reports [28–33], but data are sparse and not always congruent. Whereas some of these early reports failed to evidence any particular advantage of using MTXF for analgesia in dentistry (at that time MTXF was mainly used for sedation, like nitrous oxide), others found some benefits in its use for certain

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Table I. Inclusion and exclusion criteria for the literature search.

Inclusion criteria	Exclusion criteria
• Publications involving humans	• Animal studies
• Use of methoxyflurane for analgesic oral pain management	• Use of methoxyflurane for general anesthesia
• Publications written in English or in French	• Narrative reviews, letters to Editor, personal opinions

patients [28,30]. For conservative dentistry, Edmunds and Rosen showed that nitrous oxide caused significantly less uncooperative behavior than MTXF [33]. Regarding the extraction of third molars, Abdullah *et al.* reported that sedation with MTXF or nitrous oxide was comparable in terms of the level of anxiety [34]. In Australia, where MTXF has long been available for dental practice, some expert guidelines for the optimal use of MTXF in dentistry are available [35]. Since 2016, inhaled 3-mL MTXF (Penthrox®) has been approved in the vast majority of countries in Europe for the treatment of moderate to severe pain in adult trauma patients who are conscious [36].

Thus, a systematic review of the literature was conducted, according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) methodology [37], with the following objectives: (1) to determine the efficacy of MTXF in the management of acute oral pain, and (2) to highlight the most effective procedure suitable for oral practice.

Materials and method

Protocol and registration

This systematic review was conducted and reported according to the PRISMA 2020 statement [37]. The review was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) database: CRD42022357635.

Search strategy

A literature search was performed using the MEDLINE PubMed, Scopus, and Cochrane Library online databases covering all types of articles published in English or in French, dating from the first report of MTXF use for analgesia to December 2022.

The research strategy was carried out based on the PICO system in order to answer the following research question: What is the relevance of methoxyflurane in the management of acute oral pain?

P (participants) = Patients with oral pain (without distinction in the etiology: inflammatory, infectious, traumatic origin, *etc.*).

I (interventional) = Administration of methoxyflurane.

C (comparison) = By placebo or other analgesics.

O (outcome) = Decrease in pain.

For the MEDLINE-PubMed database, publications were retrieved using the search phrase: ("Acute Oral Pain Management"[Mesh] OR "Oral Pain Assessment"[Mesh] OR "Dental Anaesthesia"[Mesh] OR "Analgesic in Dentistry"[Mesh] OR "Analgesia in Dentistry"[Mesh] OR "Sedation in Dentistry"[Mesh] OR "Dental practice"[Mesh] AND ("Methoxyflurane"[Mesh] OR "Penthrane"[Mesh] OR Penthrox AND (English [la] OR French[la]). The Scopus and Cochrane Library databases were searched for the keywords "Methoxyflurane" and "oral pain" or "dentistry" in the title, abstract, or keywords of the articles. An additional manual search of the reference lists of the selected articles was also conducted to complete the main search.

Screening of studies and data collection

After removing duplicates, two investigators (OM, PL) independently screened the titles and abstracts of the articles. Articles were selected on the basis of the inclusion and exclusion criteria defined in Table I. The full-text articles were then assessed by the same investigators to determine publication eligibility. The selection process is detailed in the PRISMA flow diagram (Fig. 1). Any disagreement between the two investigators regarding article inclusion was resolved by a third independent author (SB).

Data were collected independently by two authors (OM, PL) and entered into an electronic database (2018 Microsoft Excel, Microsoft Corporation, Redmond, WA, USA). The following data were extracted from each selected article: (1) authors and date of publication, (2) study design, (3) country of origin, (4) characteristics of the population for test and control groups (number, sex, age), (5) inclusion and exclusion criteria, (6) procedures of MTXF administration, (7) pain assessment, (8) adverse events, and (9) satisfaction regarding MTXF use for acute dental pain management.

Assessment of risk of bias and level of evidence

The risk of bias was independently evaluated by two authors (OM, AF) using different methods depending on the study design: the Risk Of Bias In Non-randomized Studies – of Intervention (ROBINS-I) tool [38] and the Cochrane risk of bias tool for randomized trials (RoB 2) [39]. Disagreements between the two investigators regarding the risk of bias in

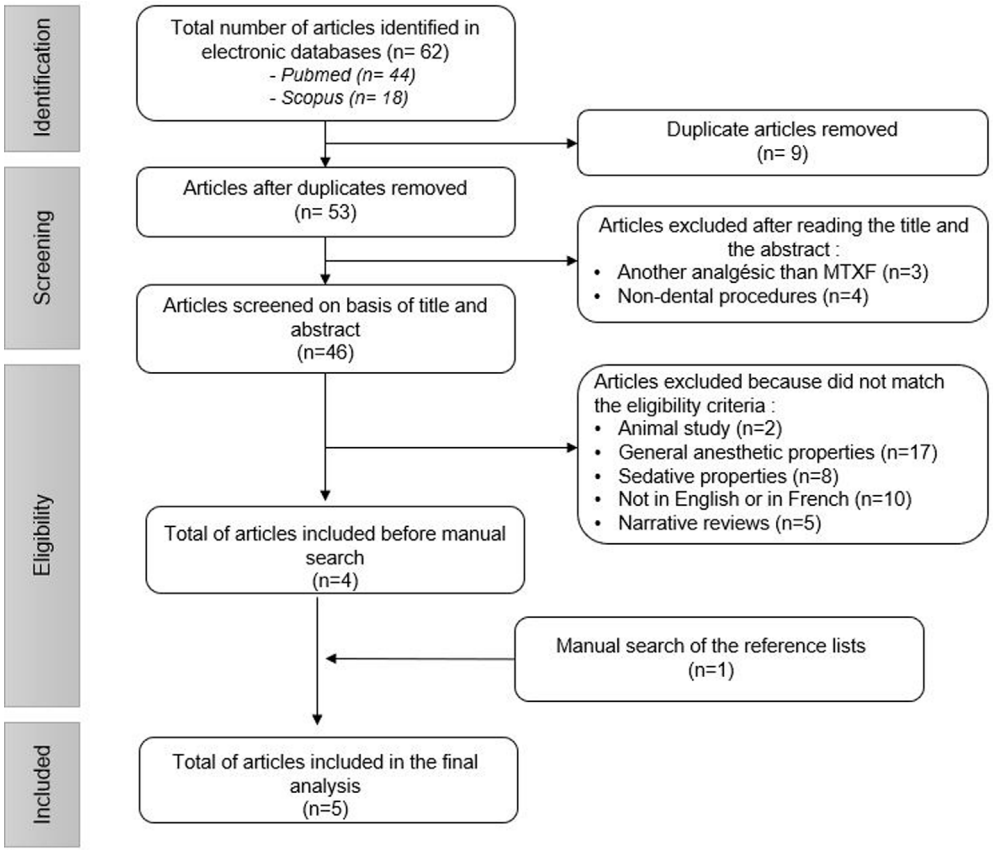

Fig. 1. PRISMA flow diagram of the literature search.

a publication were resolved by a third author (SB). The articles selected were then classified into three categories: high risk of bias when there was a "yes" score of up to 49%, moderate risk for a score of 50–69%, and low risk for a score of ≥70%. The level of evidence of each selected article was graded according to the Oxford Centre for Evidence-Based Medicine five-level scale (OCEBM), the first level being the highest one [40].

Synthesis and analysis of the results

A meta-analysis was not possible because of the heterogeneity of the included publications. Therefore, a descriptive analysis was conducted using Microsoft Excel 365 (Microsoft Corporation). For each variable, the number and percentage or the mean ± standard deviation (SD) was calculated.

Results

Search outcome

The literature search results and selection process are summarized in the flow diagram (Fig. 1). Overall, 62 publications were identified through the database search (including 44 in PubMed, 18 in Scopus, and none in the Cochrane Library). After eliminating 9 duplicates, an initial selection was made based on the titles and abstracts of the articles. Seven articles were excluded because they referred to analgesics other than MTXF or they evaluated pain relief during non-oral procedures. According to the predefined eligibility criteria (Tab. I), and after reading the full text, 42 articles were excluded for the following reasons:

- 2 were animal studies,
- 17 dealt only with general anesthesia,
- 8 investigated only sedative properties of MTXF,
- 10 were published in other languages than English or French.
- 5 were narrative reviews.

The manual search from the reference lists of the selected articles retrieved one additional record [41] Thus, 5 publications were included in this systematic review: two randomized trials [30,41] and three case series [29,42,43], which were all used for statistical analysis. Only one of the selected studies was recent [41] and investigated the current inhaler device for MTXF administration. The other studies were published from 1967 to 1972.

Risk of bias and level of evidence

The results of the risk of bias assessment are summarized in Tables IIa and IIb. The overall quality of the five included studies is relatively low with a fairly high risk of bias. Only two studies were randomized [30,41], but none mentioned allocation concealment or blinding.

Table II. Risk of bias analysis according to the ROBINS-I and RoB2 tools, respectively. H: high risk of bias, M: moderate risk of bias, L: low risk of bias.

Table IIa

	Randomization process	Deviation from intended intervention	Missing data	Outcome measurement	Statistical Analysis and Reporting	Level of Evidence
Zabolotnii and al., 2016	L	H	L	L	M	2
Allen and al., 1972	M	L	M	M	M	2

Table IIb

	Study participation	Study confounding	Intervention classification	Deviation from intended intervention	Missing data	Outcome measurement	Statistical analysis and Reporting	Level of Evidence
Oyama *et al.*, 1971	H	M	L	L	M	M	M	4
Goldstein *et al.*, 1968	H	M	M	L	H	M	M	4
Dragon and Goldstein, 1967	L	L	M	M	M	L	M	4

The three observational studies did not clearly define the characteristics of the populations included, with the exception of the study by Dragon and Goldstein, who analyzed the populations in subgroups according to their age, thus limiting the biases of confusion and participation [29]. Regarding the study by Goldstein *et al.*, a particularly high risk of bias for missing data was noted: Of the 50 patients included, only 35 were actually analyzed for the conclusion [42].

In the statistical analyses of these five studies, the risk of bias was assessed as moderate because it was expressed only by reporting mean values, with no indication of the degree of dispersion or the significance of the results.

On the basis of the OCEBM scale, no study reached a level of evidence higher than 2. Both of the randomized clinical trials, *et al.*, the studies by Zabolotnii *et al.* [41] and by Allen *et al.* [30], are graded at a level of evidence of 2, while the three observational studies are graded at a level of 4.

Characteristics of the population

The five included studies involved a total of 488 patients with a slight female majority: 58.8% female *vs.* 41.2% male participants (Tab. III). The overall mean age was 36.9 ± 8.20 years. All the studies included only adult patients

Table III. Characteristics of the five selected clinical trials.

Author (first) date of publication	Study design	Country	Population characteristics	Control groups	Inclusion criteria	Exclusion criteria	Methoxyflurane procedure
Zabolotnii, 2016	Randomized trial	Moldova	101 patients (mean age = 29.2 years, 32 F, 69 M)	Local anesthesia (41 patients)	– Adult (> 18 years) – Dental caries, pulpal diseases and wedge-shaped defects.	– Kidney or liver deficiencies – Diabetes – Pregnancy	– MTXF self-administration using an inhaler in 60 patients – 10 inhalations before opening the pulp chamber
Allen, 1972	Randomized trial	USA	52 patients (17–51 years) (31 F, 21 M)	MTXF Cyprane inhaler or MTXF Analgizer	– Restorative dentistry – Oral surgical intervention	– Patient in whom the analgesia was repeated	Continuous MTXF analgesia *via* Cyprane inhaler in 28 patients or Analgizer (closed and open) in 24 patients, from 3 L/min to 12 L/min
Oyama, 1971	Descriptive study	Japan	23 patients	MTXF Cyprane inhaler or MTXF Analgizer	Dental procedures		Increasing MTXF concentrations from 0.2% to 1.1% for 8 min in 10 volunteers and 13 dental out-patients
Goldstein, 1968	Descriptive study	USA	50 patients	MTXF inhalation using nasal cannula or nasal hood	Painful dental manipulation		Increasing concentration of MTXF from 0.1% to reach the desired concentrations: – using nasal cannula 1% in 20 patients, 1.5% in 5 patients over an interval of 90 s, and after prior 1% MTXF mask inhalation for 60 s before 1% in 10 patients – using nasal hood 1% in a group of 15 patients
Dragon, 1967	Descriptive study	USA	262 patients: 3 groups: 22 children (1–10 years), 83 adolescents (10–15 years) and 157 adults (16–67 years)		– Routine dental operative procedure or simple extraction – Patient classified as apprehensive	– Patients not classified as apprehensive	– First administration by a practitioner and then by a dental assistant using a face mask – 15 mL of 1% MTXF for 3 min and an additional 2 min in several patients

F: Females, M: Males, MTXF: Methoxyflurane, USA: United States of America.

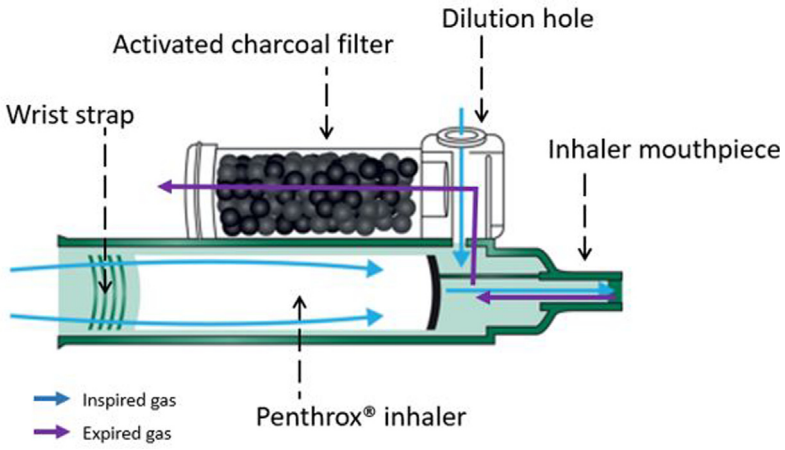

Fig. 2. Administration scheme of methoxyflurane (Penthrox®). Once added to the inhaler, the liquid methoxyflurane is absorbed through a propylene wick, vaporizes, and is inhaled by the patient through the tip. The exhalation is also done through the inhaler.

(>18 years old) except for the study of Dragon and Goldstein that also included a group of 22 children (aged from 1 to 10 years) and a group of 83 adolescents (aged from 10 to 15 years), thereby enabling subgroup analysis [29].

All of the studies included patients for oral procedures such as curettage of carious lesions, dental pulp eviction, simple tooth extraction, and restorative dentistry procedures.

MTXF administration procedures

All of the five studies assessed the use of inhaled MTXF but with sometimes different ways of administration. The Cyprane® hand-held inhaler was used in the four oldest studies [29,30,42,43]. This device was generally coupled to a full-face mask and the MTXF was administered by an investigator. One of these studies compared the use of a nasal hood and a nasal canula [42]. Importantly, this Cyprane® device is no longer marketed. The most recent study was performed using the only device currently marketed, *et al.*, the Penthrox® inhaler coupled to a facial mask that allows self-administration of MTXF [41] (Fig. 2).

All the studies investigated MTXF concentrations ranging from 0.1% to 1.5%. In two studies, MTXF was administered at a constant concentration for an initial session of several minutes before starting dental procedures and then, usually on the patient's request, for additional short sessions during the dental procedure [29,30]. In two other studies, patients received increasing concentrations of MTXF from 0.1% to 1.5% in a short preliminary step before additional sessions on the patient's request during the dental procedure [41,42].

Pain assessment

Different methods were used in the selected studies to assess the pain level of patients during oral procedures (Tab. IV). In the two oldest studies, pain levels were assessed by operators regarding the ability of the patient to undergo a complete procedure [29,42]. In the vast majority of patients, the pain level was low or very low. However, in one study it was found that an additional injection of local anesthetic was necessary in approximately 70% of the oral procedures [29]. Of note, it should be underlined that these studies aimed to compare different procedures of MTXF administration and not the analgesic efficacy of the MTXF itself. The level of pain appeared to be dependent on age, since operators noted the inability to complete dental procedures in children much more frequently than in adolescents or in adults [29].

Regarding pain assessment, the study by Oyama *et al.* investigated only the correlation between the pain threshold measured *via* the Clutton-Brock method (increasing pressure on the anterior surface of the tibia) and the arterial concentration of MTXF [43]. In the study by Allen *et al.*, approximately 84% of the patients reported low or very low levels of pain and a supplemental local anesthetic injection was necessary in only 3.84% of cases [30].

Using the available Penthrox® inhaler, Zabolotnii *et al.* [41] recorded a low or very low level of pain for approximately 85% of their patients [41]. However, this level was significantly higher than in the control group in which a local anesthetic injection was used ($p < 0.001$); an additional local anesthetic injection was required in 75% of the patients of the MTXF group, particularly for the most painful dental conditions such as juxta-pulpal caries or pulpitis.

Adverse effects

The occurrence of adverse effects when MTXF is administered for analgesia is very low. No cases of cardiac, renal, or hepatic toxicity were found in the studies. Most of the reported adverse effects are transient, self-limiting, and occurred in a minority of patients (Tab. V). The most frequently reported adverse effects were sensations of dizziness, nausea, or drowsiness and some cases of diplopia or nystagmus. Few cases of intraoperative amnesia have been highlighted in the literature [29].

Table IV. Level of pain and assessment method.

Author (first) and date of publication	Pain assessment method	Level of pain during dental procedure			
		Moderate	Low	Very low	Total patients
Zabolotnii, 2016	Patient: 10-point numeric rating scale	11.66%	63.33%	25%	60
Allen, 1972	Patient: 3-point verbal scale	15.38%	21.15%	63.46%	52
Goldstein, 1968	Practitioner: 3-point operating scale rated as "good," "fair," and "poor"	17%	63%	20%	50
Dragon, 1967	Practitioner: 3-point scale of qualifying apprehensive signs as "good," "fair," and "poor"				
	Adult	2.06%	2.54%	95.40%	157 adults
	Adolescent	6.02%	2.38%	91.60%	83 adolescents
	Child	54.54%	18.26%	27.20%	22 children

Upon cessation of MTXF administration, the effects are quickly reversible, after 15 min on average. The maximum time for full recovery was estimated at 30 min to restore normal cognitive and psychomotor functions [30,44].

No allergic reaction was listed.

Most of the time, the fruity odor of MTXF did not seem to bother patients. However, this can be unpleasant for some patients, and thus several authors advised warning patients before MTXF use [30,42].

Satisfaction regarding MTXF use for acute dental pain management

In the oldest studies using the Cyprane® inhaler, more than 90% of the adult patients reported being fully satisfied with the use of MTXF [29,42]. By contrast, only 27% of children under the age of 10 years reported satisfaction with MTXF, probably because they were more bothered by the facial mask than adults were [42].

From the perspective of the practitioner, the safety and simplicity of MTXF administration were noted by all the authors and the vast majority of practitioners were totally convinced of its usefulness. MTXF provided effective and predictable analgesia [43]. However, the use of a large face mask, which sometimes interfered with the oral procedure, resulted in dissatisfaction for some operators [30].

Discussion

This PRISMA systematic review provides an update of the use of MTXF for pain control during oral procedures in emergency care settings. This update is of importance since a device was recently marketed for pain control in some countries, the Penthrox® inhaler, mainly for emergency care settings. MTXF is one of the many agents available for pain control. Nevertheless, its use remains controversial in oral practice due to the limited and conflicting available evidence for oral pain. The poor quality of the studies included in this systematic review and the lack of strong evidence make it difficult to determine the true effectiveness of MTXF for this indication. The heterogeneity of these publications prevented any performance of a meta-analysis.

The main limitation of all of the 5 clinical trials included in this systematic review is the high risk of bias that may affect the validity of results. None of the studies were fully blinded, but were only blinded either for the patient or for the investigator. Only two of them were randomized [30,41]. In three of these studies, the sample size was clearly under-estimated [30,42,43]. Moreover, the study by Dragon and Goldstein [29] was a single-group study, whereas three of the other studies included control groups to compare different procedures of MTXF administration only and not to investigate the true efficacy of MTXF for pain control [30,42,43]. Only the most recent study assessed the sole available device to date for MTXF administration, the Penthrox® inhaler, and included a control group with an alternative pain control approach during dental procedures [41].

Table V. Adverse effects of MTXF reported in the selected literature.

Author (first) and date of publication	Kidney	Liver	Heart	Respiratory	Nausea/ Vomiting	Dizziness/ vertigo	Drowsiness	Diplopia/ nystagmus	Intraoperative amnesia
Dragon, 1967		0	0	0	0	0	0	0	27/262
Goldstein, 1968		0	0					0	
Oyama, 1971			0	0					
Allen, 1972	0	0	0	0	1/52	1/52	18/52	1/52	4/52

MTXF: Methoxyflurane.

Regarding pain control using MTXF for acute oral pain, the main limitation of this systematic review is the lack of consistency in the methods used to assess the pain level during the oral procedure: The studies differed widely in the methodology they employed. They used different scales to measure pain relief for various oral procedures with different protocols for MTXF administration. Therefore, no clear conclusions can be inferred from these studies regarding the efficacy of MTXF for acute oral pain control.

However, the analgesic efficacy of MTXF was reported in some reviews about MTXF use for dental procedures [35,45,46]. Moreover, this analgesic efficacy was evidenced in some well-designed studies of minor trauma conditions. In 2014, a British randomized, double-blind, multicenter, placebo-controlled and well-powered study demonstrated that inhaled MTXF using the Penthrox® device reduced pain severity significantly more than placebo in the short term for patients older than 12 years with minor trauma 47 [44]. This one concluded that MTXF is effective and generally well tolerated for the management of acute pain in adults and adolescents presenting to hospital emergencies with minor traumatic pain. It was the pilot study for several good practice recommendations, in particular for the French National Authority for Health [36]. These results have been confirmed by other appropriate studies in Europe and worldwide for trauma-related pain in patients admitted to hospital emergency departments [19,20,47,48]. All of these studies highlighted the fast efficacy and the safety of low-dose MTXF inhalation in a 3-mL vial for pain relief *via* the Penthrox® device in the context of minor trauma emergencies. Of note, using the same device and the same procedure for MTXF administration for dental conditions, it was found that the efficacy was not significantly different than that provided by alternative local anesthesia [41].

Besides its analgesic effect, MTXF has been shown to have sedative properties comparable to those of nitrous oxide (equimolar mixture of oxygen and nitrous oxide) for a wide range of conditions [49]. The same sedative property was also evidenced for dental conditions in a randomized crossover study of wisdom teeth extraction [34].

The low incidence of adverse effects using the MTXF protocol according to the manufacturer's instructions is undoubtedly a key factor for its safe use in pain control for minor trauma conditions, including oral conditions. Nevertheless, it is important to follow the recommendations of national drug safety agencies with regard to contraindications of MXTF use in the case of renal insufficiency, respiratory depression or cardiovascular instabilities, loss of consciousness, or hypersensitivity to fluorinated anesthetics. In addition, in France, the French National Authority for Health contraindicates the administration of MTXF in patients under the age of 18 years [36]. Nevertheless, recent European studies have proven the absence of toxicity and have shown comparable efficacy of MTXF in patients aged 12–18 years [50,51]. Interestingly, in a recent meta-analysis, adolescents were shown to have better tolerance to MTXF compared with adults, due to a higher satisfaction level and lower incidence of treatment-related adverse events [52]. Moreover, this technique seems to be appreciated by patients because they have the possibility to adapt the MTXF concentration inhaled according to the severity of pain and their level of stress [53].

Levels of occupational exposure to MTXF vapor during routine clinical practice are very low when using the current Penthrox® inhaler [54]. This offers reassurance to healthcare providers who supervises patients receiving low-dose MTXF analgesia. However, it is recommended that healthcare providers who are regularly exposed to patients using the MTXF inhaler be aware of the occupational health and safety guidelines for the use of inhalational agents [55]. Furthermore, to reduce occupational exposure to MTXF, the Penthrox® inhaler should always be used with the activated carbon chamber that adsorbs exhaled MTXF [56].

Conclusion

The use of inhaled MTXF use for pain relief during oral procedure is an emerging indication in emergency care settings. Therefore, the available data are sparse and not always congruent. This systematic review highlighted the high risk of bias of the available literature and underlined the urgent need for an appropriate and well-designed study with a high level of evidence in the specific field of oral conditions, dental practice in particular. A study of this type could be of great interest, particularly in the context of oral emergencies as an interim solution, and especially since the number of patients admitted is constantly increasing and pain is the main reason for presentation. Additionally, there is good evidence on the use of MTXF in other emergency conditions

such as minor trauma, combining favorable analgesic and sedative effects. This could therefore also make it possible to administer care in a safe and non-stressful manner, especially in view of the fact that many people have a significant fear of oral settings.

Funding

This research did not receive any specific funding.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

All data are available from the corresponding author upon reasonable request.

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Cite this article as: Mériaux O, Falguière A, Lesclous P, Boisramé A. 2024. Management of acute oral pain using methoxyflurane: a systematic review. *J Oral Med Oral Surg*. 30: 34., https://doi.org/10.1051/mbcb/2024032