Literature Review

Topic delivery of analgesics in oral surgery

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(Received: 26 June 2018, accepted: 23 February 2019)

Keywords: analgesics / topical route / oral surgery

Abstract – Introduction: Following any oral surgery procedure, postoperative pain is an inevitable outcome and can be described as moderate to severe. The pain management is essential for the comfort and the well-being of the patients. Topical delivery and more specifically transmucosal delivery systems seem to be of great value for the development of new pain management strategies. Method: A systematic literature review was performed using PubMedCentral database. Only PubMedCentral indexed publications were selected and included if they described i) a human clinical study with pharmacokinetic and/or pain relief assessment a biomaterial for topic delivery, ii) the delivery of analgesics or NSAIDs for analgesic purpose and iii) a biomaterial for topic delivery. Results: Ten articles were selected among which 4 pharmacokinetic studies and 8 studies describing pain relief. Six of the selected articles were well defined with a good scientific level of evidence (level 2) and 4 of them with a low level of evidence. Discussion: The clinical investigations demonstrated a good analgesia, a rapid pain relief with a decrease of the administered doses compared to the oral administration. Moreover, these topical analgesics were well tolerated by the patients. Number of devices was developed for the topical delivery after oral surgery procedures. Excepting a gelatin sponge and a hydro alcoholic gel, most of the devices were made of cellulose and its derivatives. Authors reported that the materials showed a good maintenance at the site of application and the release of the analgesic was well controlled over the time. Conclusion: However, well conducted large clinical trials are still missing in order to validate the absence of side effects.

1 Introduction

According to the International Association for the Study of Pain (IASP), the pain can be described as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1,2]. The pain control, notably the postoperative pain control, is essential in the management of the patient. Indeed, postoperative pain is an unavoidable outcome of any surgical procedure and pain related to oral surgery is one of the most studied. Based on the predictability of the postoperative pain, a preventive treatment is recommended by several agencies including the French Health Agency: (HAS) [1].

In 2005, this agency published guidelines for the prevention and treatment of the postoperative pain management after oral surgery. This pain is described as “moderate to severe with a maximum of pain reached after 2 to 6 h post surgery followed by a slow relief ending after 6 to 10 days” (Fig. 1) [3]. Throughout this report, the expert panel stated that the prevention of the pain should encompass the predictive parameters of its appearance and intensity. These parameters include the difficulty of the surgery, the operating capacity of the surgeon (practice) and factors linked to the patient (age, cleanliness, tobacco, anxiety, depression).

In addition, the world health organization (WHO) published a 3 steps ladder for analgesic prescription based on the pain intensity (Fig. 2) [4,5]. Moreover, for pharmacological reasons, the efficacy of the analgesics may vary depending on the analgesic used and from a patient to another. For these reasons, 2 types of prescription can be used: analgesia at constant interval or analgesia on demand of constant doses.

In pain relief treatment, it is well known that anticipated analgesia (avoiding the pain establishment) is more effective that curing. Consequently, after surgery, analgesics will be prescribed on a regular basis for 2 days (e.g. 1 g of paracetamol every 4 to 6 h), and then on demand if the symptoms remain. Several analgesic molecules can be found in the therapeutic

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panel for the treatment of post surgery pain. They can be classified in 3 steps based on their efficacy (I, II and III) or according to their family (analgesics, NSAIDs (nonsteroidal anti-inflammatory drugs), opioids).

According to the WHO, for the lower pain (visual analog scale (VAS) 0 to 4), step I analgesics should be used, and without notice, paracetamol will be prescribed to the adult at the posology of 1 g every 6 h for 3 days. Once the VAS increases above 4 (4 to 7), step II molecules should be used. Two possibilities can be chosen. In the first one, weak opioids (codeine, tramadol) are prescribed alone or combined with paracetamol. The second possibility consists in the prescription of NSAIDs alone or combined with paracetamol. Finally, in the context of high pain scores (VAS > 7), opioids alone or in combination with other analgesics are recommended (Tab. 1).

The management of the postoperative pain is mainly performed by the prescription of analgesics per os (rarely via intra venous administration). Even if this delivery route is very convenient (easy administration, low costs) and effective, it suffers from several drawbacks linked to the administration route, to the molecule used or to the patient’s compliance (Tab. 1) [6,7].

Once the analgesic is delivered by oral route, it has to overcome limiting parameters such as i) the hepatic first pass effect with degradation and removal of the drug leading to a low plasmatic concentration, ii) systemic effect and iii) the compliance of the patient. On the top of these problems, some side effects linked to the molecule used have been reported such as i) peptic ulcer, ii) gastrointestinal toxicity, iii) hepatic toxicity and iv) nausea.

One approach to overcome these therapeutic limitations is to maximize drug delivery levels at the site of action and minimize systemic exposure by administrating the drug directly at the site of injury. Topical application of analgesics at very low dose (subtherapeutic) has been demonstrated to provide analgesia compared to placebo and systemic administration of the same dose [7–9]. For these reasons, topical delivery and more specifically transmucosal delivery systems seem to be of great value for the development of new pain management strategies.

This review firstly proposes to investigate the analgesic efficiency of the topical delivery systems used for transmucosal delivery in oral surgery postoperative pain management. Secondly, throughout this manuscript, we will describe the influence of the material device used to develop delivery systems. These effects will include the properties (adhesion, release, degradability) and the pharmacokinetic of delivered analgesics.

Fig. 1. Pain intensity profile over a 7 days period of time [3]. VAS: Visual Analog Scale; D: Day.

Fig. 2. Steps ladder for analgesic prescription according to the world health organization [4]. NSAID: Non-Steroidal Anti-Inflammatory Drugs.
| Pain Step | Treatment | Posology | Side effects | Contraindications |
|-----------|-----------|----------|--------------|-------------------|
| Low       | Paracetamol | 1 g/6h (max 4 g/j) | Rare allergies | Liver failure |
| I         | NSAID     | Analgesic posology, < 72 h | Hemorrhage, digestive troubles, allergies | Asthma and allergies history, Pregnancy (≤ 6th month), Hemorrhage, Evolving ulcer |
|           | Tramadol  | 50–100 mg/6h | Nausea, vertigo, vigilance disorder | Hypersensitivity, MAOI |
|           | Paracetamol/Codeine | 60 mg pour 1 g de paracetamol/6h | Constipation, drowsiness, alertness disorders | Same as paracetamol, Respiratory failure, Children below 12 years old, Breast feeding |
|           | Paracetamol/Tramadol | 325/37.5 mg 1–2 pills/6h | Same as drugs alone | Same as drugs alone |
|           | Buprenorphine | 0.8–4 mg/j | Nausea, vomiting, head ache, insomnia | Liver failure, Respiratory failure, Alcohol consumption, Children below 15 years old |
| IIb       | Nalbuphine | 0.25 mg/kg/4h | Drowsiness, nausea, vomiting | Abdominal pain, Baby below 18 months |
|           | SNAID + Paracetamol/Codeine | Same posology as drugs alone | Same as drugs alone | Same as drugs alone |
| III        | Opioids   | Non recommended without analgesic association | Constipation, nausea, metabolic and attention disorders | Kidney failure, Lung failure, Intracranial hypertension |
|           | Antidepressant | Amitriptyline | 75 mg/j | Drowsiness, Orthostatic hypotension, Sexual impotence | Myocardial infarction, MAOI |
|           | Myorelaxant | Thiocolchicoside | 4 mg twice a day | Diarrhea, Allergy | Pregnancy, Breast feeding |
|           | Antispasmodic | Phloroglucinol/Triméthylphloroglucinol | 2 pills (62/80 mg) 3 times/j | Allergy | Phenylketonuria, Breast feeding, Pregnancy (caution) |
2 Method

2.1 Literature search

A systematic literature review was performed using PubMedCentral database into two steps. The first step was oriented towards classification using the following keywords: topic, delivery, controlled release, analgesic, oral surgery, transmucosal and mucoadhesive. The second step was performed manually to detect the missed articles in the step 1 (Fig. 3).

2.2 Article selection

PubMedCentral indexed publications were selected and included if they described i) a human clinical study with pharmacokinetic and/or pain relief assessment, ii) the delivery of analgesics or NSAIDs for analgesic purpose and iii) a biomaterial for topic delivery.

On the contrary, they were not included if they were related to i) only an in vitro study (no human clinical study), ii) the treatment of pain related to cancer, iii) the delivery of a non analgesic molecule, iv) an extra oral delivery and v) an analgesic therapy for veterinary purpose.

The authors independently extracted data and assessed study quality. The objective was to characterize the analgesia efficacy after transmucosal topical delivery. Following parameters were selected and systematically analyzed: the population studied, the sampling, the analgesia, the pharmacokinetics and the in vitro properties.

According to the HAS, the level of evidence aims to characterize the ability of a study to answer the scientific question of the paper (Tab. 2). This classification was important for the analysis and the discussion of the results from the selected articles.

Table 2. Recommendation grades and scientific level of evidence according to the HAS [1].

| Recommendations grade | Scientific level of proof from literature |
|-----------------------|------------------------------------------|
| **A**                 | Well established proof                   |
|                       | Meta-analysis of randomized              |
|                       | comparative trials;                      |
|                       | Analysis of well conducted studies.      |
|                       | Level 1                                 |
| **B**                 | Scientific presumption                    |
|                       | Not randomized well conducted            |
|                       | comparative studies;                     |
|                       | Cohort studies.                         |
|                       | Level 2                                 |
| **C**                 | Case-control studies.                   |
|                       | Level 3                                 |
| **Low scientific proof** | Comparative trials with number of bias; |
|                       | Retrospective studies;                   |
|                       | Case series;                            |
|                       | Descriptive epidemiological studies      |
|                       | (transversal, longitudinal).             |

3 Results

3.1 Bibliometric analysis

The results of the systematic literature review are summarized in Tables 3 and 4 with 10 selected articles. First of all, a systematic search using key words was performed as describe in Figure 3. The entire review has been realized through a clinical trial filter. The first key word used was “Analgesic” reaching to 59 241 articles. Then this result was filtered with a second key word “Delivery” reaching to 2257 articles, and then a third one was used (oral/buccal surgery) to get 66 articles as a result. Ultimately, inclusion (biomaterial for topic delivery, delivery of analgesics or NSAIDs for analgesic purpose and human clinical study with pharmacokinetic and/or pain relief assessment) and non selection (no human clinical study, the treatment of pain related to cancer, the delivery of a non analgesic molecule, an extra oral delivery and an analgesic therapy for veterinary purpose) criteria were applied and led to 10 articles. The manual search realized in a second step, resulted in no additional articles. Finally, the non-selection and inclusion criteria (described above) were applied to get the final
Table 3. Selected article analysis.

| Article                  | Clearly defined objectives | Comparative study | Prospective study | Randomized study | Crossed study | Double blinded study | Adapted statistical analysis | Results linked to the objectives | Clinic |
|-------------------------|----------------------------|-------------------|------------------|------------------|---------------|----------------------|-------------------------------|--------------------------------|--------|
| U.J. Moore et al. [14]  | X                          | X                 | X                | X                | X             | X                    | X                             | X 2                             |        |
| U.J. Moore et al. [13]  | X                          | X                 | X                | X                | X             | X                    | X                             | X 2                             |        |
| R.A. Dionne et al. [10] | X                          | X                 | X                | X                | X             | X                    | X                             | X 2                             |        |
| L. Perioli et al. [15]  | X                          |                    |                  |                  |               |                      |                               |                                 |        |
| I.A. Alsarra et al. [16]| X                          | X                 | X                | X                | X             | X                    | X                             | X 4                             |        |
| N. Vasisht et al. [11]  | X                          | X                 | X                | X                |               |                      |                               |                                 |        |
| K. Al Hezaimi et al. [6]| X                          |                    |                  |                  |               |                      |                               |                                 |        |
| S. Movassaghi et al. [17]| X                         | X                 | X                | X                |               |                      |                               |                                 |        |
| G. Pickering et al. [12]| X                          | X                 | X                | X                |               |                      |                               |                                 |        |
| S.R. Rajeswari et al. [7]| X                         | X                 | X                | X                | X             | X                    | X                             | X 2                             |        |

Table 4. Main information of the selected articles.

| Year | Authors                  | Delivery biomaterial                | Analgesic      | Characterizations | Clinical population | Pharmacokinetic clinical trial | Pain relief clinical trial | Feeling of the patients |
|------|-------------------------|------------------------------------|----------------|-------------------|----------------------|-------------------------------|--------------------------|------------------------|
| 1992 | U.J. Moore et al. [14]  | Methyl cellulose gels              | Aspirin        | /                 | 2 × 12 patients (Control: aspirin/oral paracetamol) | /                         | Pain decrease at the early time | Decrease of the administered dose Rapid efficiency |
| 1994 | U.J. Moore et al. [13]  | Methyl cellulose gels              | Morphine       | /                 | 12 patients (Control: oral morphine)                  | /                         | No effect                         | /                      |
| 2004 | R.A. Dionne et al. [10] | Gelatin particles and sponges      | Flurbiprofene  | /                 | 107 patients (Control: oral flurbiprofene)           | 50% decrease of the plasmatic concentration | Pain decrease Good tolerability | /                      |
| Year | Authors | Delivery biomaterial | Analgesic | Characterizations | Clinical population | Pharmacokinetic clinical trial | Pain relief clinical trial | Feeling of the patients |
|------|---------|---------------------|-----------|-------------------|---------------------|-------------------------------|--------------------------|----------------------|
| 2007 | L. Perioli et al. [15] | Bilayer cellulose/polyacrylic + cellulose/hydrotalcite | Flurbiprofene | Rapid swallowing, Good adhesion, Good maintenance on the site, Slow and sustained release, faster in vivo compared to in vitro | 5 (Control: /) | / | / | / |
| 2007 | I.A. Alsarra et al. [16] | HPMC/Carbopo 934 Films | Ketorolac | / | Rat, Mouse, Human: 68 patients (Control: placebo) | / | / | Decrease of the edema/Pain decrease |
| 2009 | N. Vasisht et al. [11] | BEMA™ (Bioerodible MucoAdhesive) FBSF (Fentanyl Buccal Soluble Film) | Fentanyl | / | 12 patients (Control: oral transmucosal fentanyl citrate) | / | / | / |
| 2010 | K. Al Hezaimi et al. [6] | HPMC/polyacrylic acid gels | Ketorolac | / | 68 patients (Control: placebo) | / | / | Pain decrease |
| 2011 | S. Movassaghian et al. [17] | HPMC et CMC tablets | Amitriptyline | The release and the mucoadhesion increase when the viscosity decreases | 25 patients (Control: placebo) | / | / | Pain decrease compared to the placebo |
| 2014 | G. Pickering et al. [12] | Hydroalcoholic gels | Paracetamol | / | 20 patients (Control: paracetamol IV et S) | Decrease of the analgesia Faster analgesia | Increase of the analgesia Slight bitter taste |
| 2015 | S.R. Rajeswari et al. [7] | HPMC films | Meloxicam | / | 60 patients (Control: /) | / | / | Pain decrease Rapid efficiency Good comfort Slight bitter taste |

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10 selected articles among which 4 pharmacokinetic studies and 8 studies describing pain relief. Six of the selected articles were well defined with a good scientific level of evidence (level 2) and 4 of them with a low level of evidence (Tab. 3).

3.2 Literature analysis

Throughout the selected literature, few materials were developed for the topical delivery of few analgesic after oral surgery procedures. Most of the materials used to prepare the delivery device were cellulose-based polymers. However, couple of other materials were used.

In 2004, Dionne et al. developed a strategy to optimize the concentration of flurbiprofen at the site of interest [10]. Toward that goal, they prepared gelatin-based capsules loaded with flurbiprofen. These loaded capsules were then embedded within a gelatin sponge and placed into tooth socket after third mandibular molar surgery. They evaluated the applicability of their strategy by studying the clinical efficacy and the pharmacokinetics of their material within a double-blinded clinical study including 107 patients over a 6 h postoperative period of time. This clinical trial revealed a higher and faster analgesia associated with a lower plasmatic concentration (50% reduction) of their structures compared to the oral administration (per os). Moreover, this new strategy has been revealed to be well tolerated by the patients. Two other studies on materials other than cellulose have been realized. The first one, published by Vasisht et al. in 2009, evaluated the pharmacokinetics of a buccoadhesive bilayer material loaded with fentanyl called BEMA® (BioErodible MucoAdhesive) [11]. Unfortunately, no pain relief monitoring has been done. The last study, realized by Pickering et al. in 2014, was based on the use of a hydroalcoholic solution of paracetamol and compared to intravenous and sublingual administration [12]. The results demonstrate a higher and faster analgesia compared to the controls. Moreover, the pharmacokinetic investigation demonstrated a lower amount of paracetamol in the blood stream when the analgesic was administered topically.

As mentioned previously, most of the materials used to develop intra oral delivery device was the cellulose and its derivatives (methyl cellulose and carboxymethyl cellulose). However, the leading polymer used was the hydroxypropyl methylcellulose (HPMC). Indeed, three studies have been published using cellulose or methylcellulose and four clinical studies have been published using HPMC-based materials for the topical delivery of analgesics. Indeed, three studies have been demonstrated a lower amount of paracetamol in the bloodstream when the analgesic was administered topically.

The clinical trials demonstrated a high and rapid analgesia. Moreover, a decrease of the molecular weight of the polymers and HPMC/CMC ratio, plays a crucial role. Indeed, the increase of the concentration of CMC leads to a decrease of the stiffness and an increase of the fragility. Therefore, a decrease of the concentration of CMC of 60% decreases the amount of adhesivity of the material while favoring the release of the amitriptyline from 60 to 100%. More recently, in 2015, Rajeswari et al. described a mucoadhesive patch made of HPMC loaded with meloxicam for pain relief after periodontal surgery [7]. The clinical trial was a prospective double blind randomized study conducted on a 60 patients population divided in 4 groups (10, 20, 30 and 45 mg of meloxicam). They described a good pain relief and a rapid efficiency. It is worth noted that their patients mentioned a good comfort and that they patients spontaneously asked for the use of this analgesia device for later surgeries.

Throughout these studies, it has been shown that cellulose-based materials presented good adhesion properties with a maintenance at the site for the duration of the investigation. The clinical trials demonstrated a high and rapid analgesia.

4 Discussion

4.1 Pain relief

The selected articles reported a good pain relief associated a rapid efficiency of the analgesic. However, in one study, Moore et al. described the delivery of morphine using a methylcellulose gel after mandibular third molar removal. No analgesia has been reported and an escape painkiller has been administrated [13]. This failure has been explained because of no peripheral effect of their device. One of the explanations might be the low number of opioid receptors within the oral mucosa and also the lack of activity of these receptors. The lack of efficacy is due to the use of morphine rather than the device itself. Indeed, in a previous article, Moore et al. demonstrated the analgesic efficacy of their structure associating a methylcellulose gel with 2 different analgesics (aspirin and paracetamol) [14].
Globally, the clinical evaluations of the topical delivery of analgesics demonstrated the good comfort of the patients using these delivery devices.

### 4.2 Delivery device

For the design of intra oral delivery device, the material used can be from wide origins with natural (polysaccharides, proteins) and synthetic (polyvinyl alcohol, polycrylic, alcohol, polyethylene glycol) polymers. However, on a clinical point of view, only a few of them have been evaluated. The main part of polymer used is composed of cellulose and its derivatives (cellulose, methylcellulose, carboxymethyl cellulose (CMC) and hydroxypropyl methylcellulose HPMC), which are formulated alone or with a copolymer [6,7,13–17]. The formulations aim at optimizing the encapsulation of the analgesic while controlling its leakage. They also should enhance the bioadhesivity onto the oral mucosa and maintain their integrity for a period of time compatible with the pain profile. Indeed, a large number of enzymes can be found in the oral cavity including aminopeptidases, carboxypeptidases, deshydrogenases and esterases which can degrade the polymer-based devices limiting their life time and therefore the controlled release of the analgesic over a long period of time.

### 4.3 Mucosa adhesion

Besides the protection, the remaining of the device on the site is a key factor for the success of such a strategy. Consequently, the use of mucoadhesive polymer is essential to maintain an intimate contact between the delivery device and the mucosa. Mucoadhesion is a complex phenomena and a number of theories has been argued such as a mechanical interlocking, diffusion/interpenetration, electrostatic interactions and adsorption [18]. Nowadays, the most studied theory is the formation of hydrogen bindings between the material and the mucosa [19]. Toward that goal, the materials used are mainly prepared with hydrophilic polymers incorporating functional groups with high potential of hydrogen bonds. The functional groups capable of such bindings can be hydroxyl, carboxyl and amine groups. These functions are found in a large amount within the synthetic polymer family and even more in polysaccharides such as cellulose (CMC, HPMC). This last one has demonstrated a great property of hydration in humid media and the possibility of making hydrogel structures, which can interact with the superficial layer of the mucosa creating a hydrogen bond network leading to the adhesion of the material onto the mucosa.

### 4.4 Drug release

Once administered, the device should allow the sustained release of the entrapped drug. Even if numerous *in vitro* studies, about the controlled released of drug from biomaterials, have been published, only 2 have been selected about the *in vivo* release of analgesics. Perioli *et al.* studied the properties of bilayer tablets [15]. They demonstrated a rapid swallowing, however, the behavior of their structure seemed to act differently once applied *in vivo*. Indeed, the constitution of the saliva combined with the friction forces leads to an increase of the erosion. These phenomenon lead to a constant release over the time and to an increase of the maximum rate of release of the encapsulated molecule enabling a sustainability local concentration. In addition, Movassaghian *et al.* demonstrated that the increase of the concentration of CMC leads to a decrease of the stiffness and an increase of the fragility and a decrease of the molecular weight of the HPMC induces an increase of the adhesivity of the material while favorating the drug release [17]. These properties could be explained by an increase of the hydrophilic leading to a better swelling of the material and to a higher diffusion within the scaffold. This last property is essential regarding the wettability and consequently to the adhesion onto the mucosa and on the release profile of the loaded drug.

In addition, it is worth noted that few authors such as Perioli *et al.* developed bilayered structures in order to promote the mucosa adsorption and to prevent the release of the analgesic into the oral cavity [15].

### 4.5 Drug delivery and diffusion

Despite the difficulties (saliva, mechanical stress, pH, enzymes), the oral mucosa is an administration route of great interest. Because of the high vascularization, the molecule diffusing through the mucosa have a direct systemic action avoiding the hepatic first pass effect which strongly reduce the bioavailability of the drug administered orally [9]. Number of authors have been studied the mucosa permeability and stated that oral mucosa presents a permeability 4 to 4000 times higher compared to the skin [20]. The molecules can be transported through the epithelial via passive diffusion, active transportation and specialized systems. The published studies stated that the main route for transportation is the passive diffusion of molecules through transcellular and paracellular routes [21–23]. The hydrophilic properties of the paracellular route seams to act as a barrier for hydrophobic molecules but is the main route for hydrophilic molecules. On the contrary, the transcellular route requires the crossing of cellular membrane (lipid bilayer membrane) and consequently represents a favorable route for hydrophobic drugs. Indeed, according to their amphiphilic properties, the molecules are able to use both routes simultaneously. From these findings, it is clearly stated that the pharmacokinetics of the analgesic encapsulated delivery devices should be monitored. Only 3 studies evaluating the pharmacokinetics properties have been selected. Usually, the doses of analgesics administered by locally are lower than the doses of analgesics per os [10–12]. Therefore, it is difficult to compare the plasmatic concentrations. Nevertheless, it seems clear that the analgesic absorption time is faster when used in local delivery compared to per os administration. On the contrary, Vaisiht *et al.* published a pharmacokinetisk study measuring the maximum concentration, the cumulated concentration and the absorption time of fentanyl delivered by buccal soluble film [11]. They have demonstrated that, at the same dose; the plasmatic concentration of fentanyl is
higher when a buccal film is used. Moreover, the absorption time decreases demonstrating a faster systemic diffusion of the fentanyl.

### 4.6 Limits and bias

Throughout this review, it has been revealed that the use of local delivery device for the administration of topic analgesia represents a great future in postoperative pain management. However, a number of limits has been noticed. It suffers from the lack of well conducted clinical trials. Indeed, the size of the studied population is too small to reach a good representativity. Moreover, the authors usually used placebo as control instead of the commonly used treatment (paracetamol *per os*).

Consequently, it would be of great interest to set up a well set, large clinical trial to increase the power of the study and using well defined parameters such as the analgesic control.

### 5 Conclusion

Throughout these data, the clinical interest is clear for the local delivery of analgesic for the pain management in oral surgery. This systematic literature review led to a selection of 10 original articles of which 8 of them about a clinical trial of pain management after oral surgery. Seven of them led to the conclusion that their delivery devices allow a significant pain relief. Moreover, the authors mentioned that their device provide a rapid pain relief with great efficacy at the early time. Only one article mentions a failure of this strategy.

Finally, 3 studies reported the acceptance and the well-being of the patients using this strategy [7,10,12]. Even if a bitter taste has been mentioned, the patients are satisfied of the analgesia of the device but also of the comfort and the absence of repeated drug taking. Rajeswari et al. even reported that the patients, who went under topical analgesia after surgery, requested spontaneously the same analgesia during the following procedures [7].

The results demonstrated a good analgesia of these structures with a decrease of the administered doses compared to the oral administration. Moreover, these topic analgesics are well tolerated by the patient. However, well conducted large clinical trials are still missing in order to validate the absence of side effects. A development phase will also be necessary to decrease the cost of such a strategy in order to make it applicable in oral surgery daily practice.

### Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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