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Title – Tolerance of Fentanyl Pectin Nasal Spray for procedural pain in geriatric patients

Author names and affiliations

Laurentine Maljean¹, D Pharm, Gaëtan Gavazzi², MD, PhD, Prudence Gibert³, D Pharm, Armance Grevy³, D Pharm, Marion Payen³, D Pharm, Nabile Zerhouni², Théophile Tiffet⁴, MD, Jean-Luc Cracowski⁴, MD, PhD, MD, Nathalie Mitha², MD, Caroline Maindet², MD, Magalie Baudrant³, D Pharm, Pierrick Bedouch³, PhD, Sabine Drevet², MD, PhD

¹ Pharmacy resident, University Hospital Grenoble-Alpes, Grenoble, France

² Clinician, University Hospital Grenoble-Alpes, Grenoble, France

³ Pharmacist, University Hospital Grenoble-Alpes, Grenoble, France

⁴CIC, University Hospital Grenoble-Alpes, Grenoble, France

Corresponding author

Gaëtan Gavazzi, MD, PhD, University Hospital Grenoble-Alpes, Grenoble, France, e-mail address : ggavazzi@chu-grenoble.fr, Telephone number: 00 33 4 76 76 67 60

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Brief summary: We aimed to assess the tolerance of Fentanyl for procedural pain in geriatric patients. Fentanyl tolerance was similar to the literature in younger patients. Fentanyl is a promising lead for procedural pain treatment in geriatric patients.

Acknowledgement: We wish to thank all the health professionals who helped in our study, spatially the nurses, the physical therapists, pharmacy resident and medicine resident.

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Abstract.

Objectives: We aimed to assess the tolerance of Fentanyl Pectin Nasal Spray (FPNS) when used to treat procedural pain caused by wound dressing or physiotherapy in patients older than 75 with or without opioid background treatment.

Design: This is a prospective monocentric, non-controlled, non-randomized study conducted from December 2014 to October 2017 in two geriatric wards (rehabilitation and acute medicine).

Setting and Participants: Fifty-seven patients were included and 314 procedures were monitored.

Methods: For each patient 6 procedures were monitored: the first two without specific treatment, then fentanyl was started at 100µg with a titration over a few procedures up to 800µg in non-naïve patient and 400µg in naïve. Sedation and respiratory scale were monitored during the procedures. All adverse drug events occurring from inclusion to five days after the intervention were collected and their imputability was assessed separately by two pharmacovigilance experts.

Results: 14.4% of the sessions with FPNS administration resulted in adverse drug events.

Main adverse drug events were Nausea and Vomiting, somnolence and confusion. Most of them were of mild to moderate gravity. Four severe adverse events were due to accidental overdoses. No unexpected adverse event occurred. Tolerance was similar for naïve and non-naïve opioid patients (p-value = 0.93).

Conclusion and implications: FPNS was overall well-tolerated in geriatric patients. Given its interesting pharmacokinetics, Fentanyl is a promising lead for procedural pain treatment in geriatric patients, even those who are opioid naïve.

26

27 Introduction

28 Procedural pain (PP) is defined as unintentional short-lived and acute pain, associated
29 with medical investigations and treatments conducted for the purpose of health care. PP is
30 induced by procedures such as turning, cleaning, physiotherapy or wound dressing. PP can
31 lead both immediate and long-term harmful effects, including fear, anxiety, aggressive
32 behaviour, distrust of caregivers and refusal to consent to further procedure resulting in
33 worsening patient's condition.¹ A study on 684 patients in two French hospitals showed a
34 high prevalence of PP with 55% of the patients who experienced pain during procedures.² The
35 pain was severe to extremely severe in 57% of cases. However, PP is predictable and can be
36 anticipated, prevented and minimized if not eliminated.³ Although well documented in
37 children, there is a lack of consensus about PP in adults and especially in elderly patients.

38 Geriatric patients combine several PP risks factors. Firstly, they are particularly
39 exposed to painful procedures (wound care, mobilisation, and physiotherapy) due to the care
40 of comorbidities and multimorbidities.⁴ Besides, the prevalence of osteoarticular pain is high
41 in this population maximizing the risk of pain during procedures.⁵ Secondly, aging causes
42 many pharmacokinetics and pharmacodynamics changes, making geriatric patients more
43 susceptible to adverse drug events (ADE).⁶ Thirdly, symptomatology of pain can be atypical
44 with difficulty in expressing pain. Therefore, pain evaluation is particularly complex in this
45 population, requiring the use of appropriate scale of auto and hetero-evaluation.⁷

46 Oral Short Acting Opioids (OSAO) such as morphine or oxycodone are commonly
47 used for PP management.¹ However, the ideal analgesic should meet several criteria: 1/ be
48 fast-acting to be effective, 2/ cover all the duration of the procedure (about 1 hour) and 3/
49 have a short enough duration of action to minimise side effects.⁸ OSOA's peak of efficiency is
50 1 hour to 1 hour and a half and their effect can last up to 3 to 6 hours.⁹ On the other hand,

51 Fentanyl is a synthetic opioid, μ receptor agonist, highly lipophilic, 50 to 100 times more
52 potent than morphine. Fentanyl Pectin Nasal Spray (FPNS)'s peak of efficiency is quickly
53 reached (15 minutes) and the duration of analgesia is 1 hour. Also, if analgesia is not reached,
54 it is possible to administer a second dose in the other nostril 15 to 30 minutes after the first
55 one. Therefore, pharmacokinetics of FPNS seems interesting for PP management allowing an
56 administration shortly before the procedure and the possibility to adapt the dose during the
57 procedure.^{10,11}

58 FPNS has been commercialised in France in 2010 but intranasal route was already
59 used for several years by inhaling intravenous Fentanyl.¹² Its current indication is
60 "management of breakthrough pain in adults who are already receiving maintenance opioid
61 therapy for chronic cancer pain".¹³ However FPNS use has also been reported in patient
62 without cancer: postoperative or acute pain treatments, children and adults in pre-hospital and
63 hospital setting.^{10,14} In addition, FPNS use has been suggested for the management of wound-
64 related PP in advanced illness.¹⁵ To our best knowledge, FPNS has never been investigated in
65 the management of PP in non-cancerous geriatric patients.¹⁶ The main objective of our study
66 was to assess tolerance of FPNS in PP induced by wound dressing and physiotherapy, in
67 geriatric hospitalized patients, with or without background opioids treatment.

68

69 Methods

70 Ethic approval

71 The present study was approved by the hospital ethic comity, the French national drug safety
72 agency and registered in the European Union Drug Regulating Authorities Clinical Trials
73 Database (number 2014-003156-31). Informed consent in writing was obtained from all
74 participants.

75

76 Protocol

77 This monocentric, non-controlled, non-randomized study was conducted from December
78 2014 to October 2017 in two geriatric wards (rehabilitation and acute medicine) of a French
79 University Hospital.

80 Patients older than 75 who experienced moderate to severe pain, assessed by a Visual Analog
81 Scale (VAS) $\geq 4/10$, during wound dressing or physiotherapy were eligible.¹⁷ Exclusion
82 criteria were instable bone fracture, non-communicating patient (delirium or impossibility to
83 assess pain with VAS), contraindication to opioids, drug interacting significantly with FPNS
84 or be under legal protection.

85 For each patient, six sessions of care inducing pain were monitored (see figure 1). No FPNS
86 was given during the first two sessions. If the VAS was $\geq 4/10$ at any point during both
87 sessions, the patients were included and FPNS was introduced. FPNS was administrated by
88 the nurse 10 minutes before the beginning of the procedure. A second dose was administered
89 by the nurse 5 minutes after the beginning of the procedure if the VAS was still superior to
90 4/10. A Procedure lasted between 20 to 30 minutes, up to 1 hour for some difficult wound
91 care. FPNS could be titrated over procedures, starting with 100 μ g, with the possibility of
92 increasing dosage over successive procedures according to pain assessments up to 400 μ g for
93 opioid naïve patients and up to 800 μ g for non-naïve patients. Titration protocol is available in
94 supplementary data.

95 A training on the use of FPNS was provided to the nurses before and regularly proposed
96 during the study.

97

98 Outcome criteria

99 The main objective of the study was to assess tolerance of FPNS in PP induced by wound
100 dressing and physiotherapy, in geriatric hospitalized patients, with or without background

101 opioids treatment. The first criterion was the prevalence of ADE imputable to FPNS given by
102 percentage of seances with ADE according to pharmacovigilance experts. Secondary
103 objectives were 1/ description of the ADE, 2/ prevalence of ADE according to FPNS dosage
104 and 3/ prevalence of ADE in naïve opioid patient and non-naïve.

105

106 Outcome measures

107 The Outcome measures were adverse events, sedation, and impact on the respiratory tract.

108 - All adverse events occurring from inclusion to five days after the intervention were
109 collected by asking patients before each care and five days after the last care: “have you
110 had any issues since last care?” and collecting spontaneous reports to the nursing staff.
111 The ADE were classified from grade 1 to 5 according to Common Terminology Criteria
112 for Adverse Events (CTCAE) classification.¹⁸ The causality assessment of ADE to FPNS
113 was assessed independently by two pharmacovigilance experts using Naranjo algorithm.
114 The Naranjo algorithm is a 10-question score that allow assigning probability of causal
115 relationship between medications and adverse events: ‘definite’, ‘probable’, ‘possible’,
116 and ‘doubtful’.¹⁹ All discrepancy among experts were resolved by consensus. Patients
117 discharged from the hospital within 5 days after procedure were reached by phone for the
118 last ADE collecting.

119 - Sedation and impact on the respiratory tract were measured with Ramsay scale and
120 respiratory scale respectively before the care (t0), after 15 minutes and 30 minutes of the
121 care, and, 30 and 60 minutes after the end of care (see figure 2).^{20,21} The patients were
122 considered overdosed when sedation scale was superior to 4/6 or respiratory rate inferior
123 to 10 breaths per minute. An overdose protocol based on naloxone was available: the
124 nurse or the physiotherapist would stop the procedure, alert immediately the physician and
125 oxygen and naloxone could be administered.

126 - Pain was assessed using VAS before the procedure (t0), 5 minutes after the beginning
127 (t15), 20 minutes after the beginning (t30) and a hour after the end of the procedure
128 (rec60).

129

130 Statistics

131 The variables collected to describe the studied sample were: gender, age, height, weight, type
132 of procedure, mini mental state examination (MMSE) and analgesic treatment.²² Descriptive
133 analysis was conducted on all variables collected. Qualitative parameters were expressed in
134 numbers and percentages. Quantitative parameters were described by the mean, and by
135 median with the 25th and 75th percentiles. Those data did not follow a normal distribution so
136 standard deviation could not be calculated. We used Chi-squares and fisher test (for lower
137 samples) to compare ADE rates.

138

139 Declaration of source of funding

140 This work was supported by Kyowa Kirin Pharma. Our sponsor had no role in the design,
141 execution, analysis and interpretation of data, or writing of the study.

142

143 Results

144 Population

145 Among the 57 patients included, average age was 88 years old (median 89, interquartile range
146 [84-93]), female gender represented 72% of the total population. Population characteristics
147 are detailed in Table 1. During the hospitalization, almost all patients had acetaminophen
148 (95%) and 42 patients (74%) had opioid background treatment: fentanyl, morphine or
149 oxycodone. A total of 314 sessions were monitored, 113 (36%) without FPNS and 201 (64%)
150 with FPNS: 105 with 100 µg, 84 with 200 µg, 10 with 400 µg and 2 with 800 µg.

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Global ADE

ADE imputable to FPNS occurred in 14.4% of the 201 FPNS sessions. Twenty-seven patients experienced AE (47.3% of all patients). Forty-two ADE were found imputable to FPNS since more than one ADE could occur in the same session and two ADE lasted 2 sessions. Main side effects were nausea and vomiting (6.0% of all sessions), somnolence (4.5%) and confusion (2.0%) (Table 2). These adverse events were of mild to moderate gravity (CTCAE 1 or 2). Two patients (3.5%) disrupted the treatment because of nausea. Two patients (3.5%) experienced ADE in sessions without FPNS use. No local ADE related to the intranasal administration were reported. Respiratory scale and Ramsay scale were normal except for four overdoses. Median respiratory scale was 0 (quartile 0 to 0) and median Ramsay scale was 2 (quartile 2 to 2). All ADE and their gravity are detailed in supplement 2 with the opinion of pharmacovigilance expert upon their imputability to FPNS.

The secondary objective was to describe the ADE. Four patients (7.0%), including one opioid naïve patient, experienced severe adverse events:

- one patient experienced Cheyne-Stoke dyspnea after FPNS 100µg administration. His transdermal Fentanyl had recently been increased to 37µg. FPNS treatment was resumed 4 days later with reduced dose of transdermal Fentanyl without complication.
- three accidental overdoses:
 - o one opioid naïve patient accidentally received 400µg instead of 100µg causing major somnolence for one hour after the procedure. Treatment was resumed at 100µg the next day without complication.
 - o one patient received 100µg of FPNS, he overdosed during his fifth procedure. His background treatment was 37µg of transdermal Fentanyl and 5mg of oral

176 immediate release oxycodone was administered to the patient prior to the
177 procedure. Oxygen and Naloxone were administered, and the treatment was
178 resumed four days later after a diminution of the transdermal Fentanyl without
179 complication.

180 ○ one patient overdosed after receiving an increased dose of 400µg during his sixth
181 procedure. 5mg of immediate released oxycodone was also administered to the
182 patient prior to the procedure. Oxygen and Naloxone were needed as well.

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184

185 Treatment interruption:

186 Seventeen patients (29.8%) finished the follow-up earlier: 11 for early discharge or pain
187 disappearance, 4 for alteration of general status unrelated to FPNS use and 2 due to nausea.

188

189 FPNS tolerance according to FPNS dosage:

190 ADE occurred in 14.3% of sessions with 100µg of FPNS, 13.1% with 200µg and 30.0% with
191 400µg. Two patients had 800µg and no ADE appeared. The rate of ADE with the 400µg
192 dosage was not significantly higher than the rate of ADE with a lower dosage of FPNS (p-
193 value = 0.2).

194

195 FPNS tolerance in naïve opioid patients:

196 Fifteen patients had no concomitant opioid treatment. They had 57 sessions: 32 with 100µg,
197 19 with 200µg and 3 with 400µg. Seven sessions resulted in ADE (13%.0). There was no
198 statistical difference between ADE rate between naïve opioid patients and experienced opioid
199 patients (p-value = 0.93). The ADE profile was similar to non-naïve opioid treatment except
200 for two patients who experienced constipation versus none in the non-naïve opioid group.

201 Concerning the impact of FPNS dosage in those patients, ADE occurred in 9.4% of sessions
202 with 100µg of FNPS, 10.5% with 200µg and 66.7% with 400µg. The rate of ADE with the
203 400µg dosage was not significantly higher than the rate of ADE with a lower dosage of FPNS
204 (p-value = 0.09).

205

206 Impact on VAS:

207 Before FPNS administration, the mean VAS score was 4 (median 4, quartiles 0 to 6). It was
208 the same for the first two sessions without FPNS and the sessions with FPNS. Thirty minutes
209 after FPNS administration, and 20 minutes after the sessions begin, mean VAS score was 7
210 (median 7, quartiles 5 to 8) during sessions without FPNS and 5 (median 6, quartiles 3 to 7)
211 for the sessions with FPNS. VAS mean with FPNS was significantly lower than VAS mean
212 without FPNS (p-value <0.05).

213

214 Discussion:

215 Our study investigated tolerance of FPNS in PP induced in geriatric hospitalized patients.
216 ADE occurred in 14.4% of the sessions of wound dressing and physiotherapy. ADE observed
217 were those usually expected with opioid use. For the low doses of 100 at 200 µg, the rate of
218 ADE was similar in the naïve opioid group to the non-naïve opioid group.

219 Clinical research on pain management in geriatric patients are meagre. Age-related
220 physiological changes and multi-morbidity bring complexity to the diagnostic and therapeutic
221 management phases. PP is still under-treated and under-considered. Two studies showed that
222 only 8 and 25% of the patients received analgesic before painful and wound care
223 respectively.^{23,24} The lack of knowledge of geriatric specificities and assessment difficulties
224 lead to under-diagnosis of pain in the elderly patient and to poor pain management. PP
225 management is limited by patient-specific factor, notably patient's difficulty in expressing

226 pain. Nevertheless, one of the major limiting factors is the lack of knowledge for health care
227 professionals (HCPs) in screening, assessment, and treatment of PP. This study is to our best
228 knowledge, the first study to examine FPNS tolerance in old-old patients (mean age 88
229 years).²⁵

230 Although the number of patients who experienced ADE seems high (47.3% of all patients), it
231 is in fact comparable to the tolerance of younger population in literature.²⁶⁻³⁰ In those studies,
232 the rate of ADE varied between 12 and 51% of patients. The rate of serious ADE was also
233 similar to our study. Moreover, it is interesting to note that these ADE generally did not last
234 more than one hour and were from mild to moderate gravity. The similar rate of ADE rate
235 between frail patients and younger population could be partly explained by the precaution in
236 drug dosages prescribed in the older population: therefore, we used lower drug dosage and
237 only eight patients (14%) of our study needed a higher dose than 200 μ g (12 sessions).³¹
238 According to the summary of product characteristics, FPNS should only be used with a
239 background opioid treatment superior to 60mg of morphine equivalent. The rate of AE in our
240 study was similar in naïve opioid patients and experienced opioid patients (p-value = 0.93).
241 However, although not statistically significant, the rate of ADE seemed to increase with
242 400 μ g of FPNS, especially for naïve-opioid patients. Therefore, the titration phase should be
243 very progressive.

244

245 In our study, the accidental overdoses could be linked to a short window between the OSAO
246 and the FPNS administration. Therefore, if OSAO has been administrated just before the
247 procedure, FPNS should probably not be used. The fourth severe ADE was due to a
248 medication related error: 400 μ g of FPNS was administered to a naïve opioid patient instead of
249 100 μ g. There was no consequence for the patient who resumed FPNS normally the next day.
250 FPNS has two presentations quite similar, one of 100 μ g and one of 400 μ g. To prevent further

251 events, the two dosages presentations were separated in the narcotic storage. Also, it could be
252 interesting to limit FPNS use in opioid naïve patients to 200µg. It would also prevent any
253 confusion between the two presentations and increase safety in use.

254

255 Our open labelled study was unblinded and without witness group. However, FPNS has been
256 proven safe and well tolerated compared to other rapid onset opioids for treatment on
257 breakthrough pain.^{28,32} Extrapolating the results, FPNS use could also be interesting for PP in
258 out of hospital setting (nursing home, home hospitalization...) in improving the organization
259 of caregivers's work. PP management need to consider the time of action of the painkiller and
260 care planning, which could represent a major organisational issue. With its rapid onset of
261 action, FPNS use greatly facilitated the ward work and was easily integrated in the health care
262 organizations. Moreover, on the contrary to OSAO, Fentanyl is mostly eliminated by hepatic
263 route so the risk of accumulation in case of renal deficiency is minor. Fentanyl is also
264 recommended in cirrhotic patients as it's elimination half-life seems to be unaltered.³³
265 Intranasal route is also a good alternative for patient with low venous capital or dysphagia
266 which is frequent in geriatric. Accordingly, FPNS could be a good alternative to
267 oral/intravenous opioids analgesia in the prehospital and hospital setting.¹⁰

268

269 FPNS tolerance is attractive for its use to reduce PP during wound dressing and physiotherapy
270 in geriatric population but its prescription should be secured. Following the American opioid
271 crisis, Fentanyl utilisation has increased exponentially in the last few years in Europe and in
272 France with a high risk of misuse.³⁴

273 This is a proposition of a few rules to provide a framework for FPNS use in geriatric
274 population for PP management:

- 275 - Controlled environment. FPNS indication should be limited to a secured environment
276 where Naloxone can be rapidly available if needed.
- 277 - Caregivers' education. Nursing staff trainings should be organised on FPNS use, ADE
278 monitoring and overdoses handling.
- 279 - Limited dose. FPNS should be started at a 100µg dose and carefully increased until the
280 optimal dose is found. The lowest efficient dose should be used and FPNS dose should be
281 limited to 200µg in naïve opioid patients.
- 282 - Adverse Events premedication. Frequent and well-known ADE should be anticipated.
283 Laxatives in combination with opioids is one of the start criteria. Antiemetic if needed
284 should be systematically prescribed with opioids.³⁵
- 285 - Pain assessment. Pain intensity should be regularly reassessed to ensure that patient's pain
286 is well controlled and that FPNS is still needed. Indeed, as the patient state improves,
287 procedures can become less painful.
- 288 - Short duration. To minimize the risk of addiction, FPNS prescription should be as short as
289 possible.

290

291 The low number of patients was a limitation in our study and it was related to the difficulty of
292 including patients: the short length of hospitalisation and the incidence of cognitive
293 impairment in elderly hospitalized patients made it difficult to meet the inclusion criteria,
294 notably signature of the consent form and the use of VAS to assess pain. In cognitive
295 impaired patient, capacities to express, understand and participate to pain self-assessment can
296 be impaired. The treatment of PP is even more challenging due to manage pain assessment. In
297 this case, numerical scale (self-assessment scale) used for all patients could have been
298 supplement by Algoplus scale (hetero evaluation), validated, and recommended for « non-
299 communicative » patients.³⁶

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Conclusions and Implications

To conclude, FPNS has an interesting profile of tolerance in geriatric patients. Our prospective study showed that ADE occurred in 14.4% of the sessions of wound dressing and physiotherapy in geriatric patient. Given the frequency and consequences of PP, especially the risk of rupture in patient care, FPNS shows a good risk-benefit assessment in PP amongst elderly population. This study however underlines the need for a secured framework for FPNS use. Prescription has to be reassessed and personalized to each patient's pain and tolerance. Additional data on FPNS efficiency and caregiver and patient's satisfaction will be presented subsequently.

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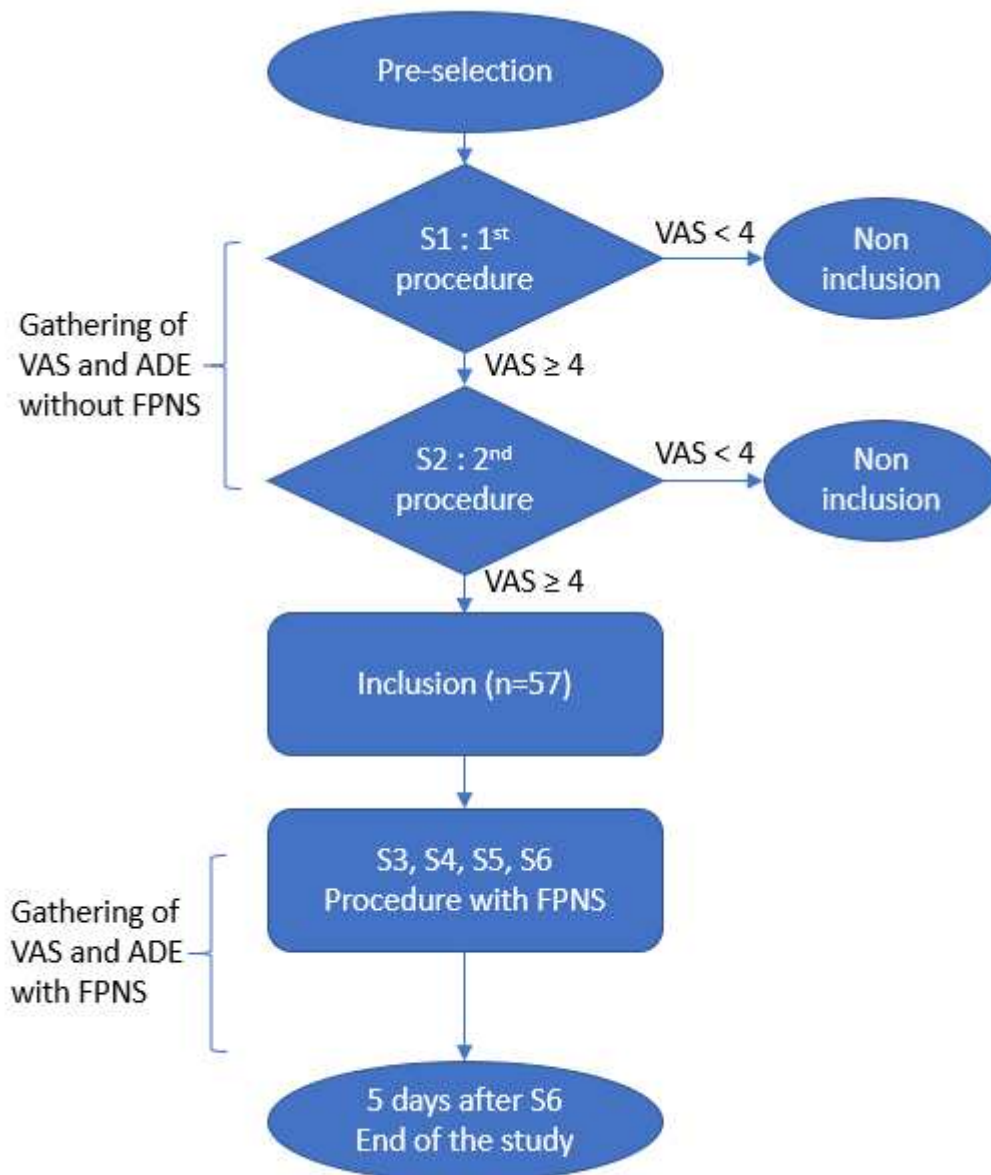
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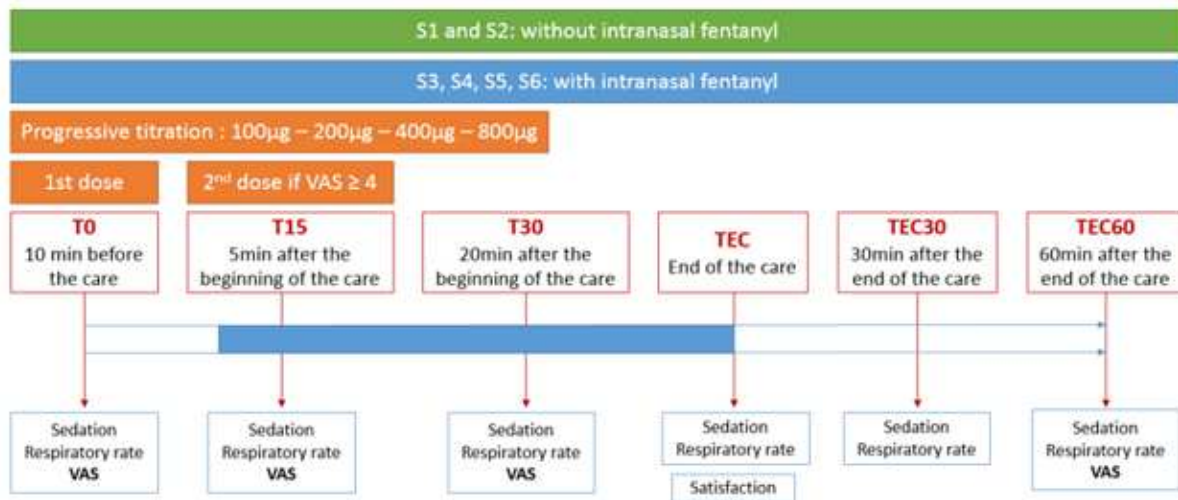
- 395 Figure 1: Study's flow chart
- 396 Figure 2: Procedure course including outcome measures.
- 397 Table1: Population characteristics
- 398 Table2: Prevalence of AE
- 399
- 400 Conflicts of interest: There are no conflicts of interest

Figure 1 : study's flow chart



VAS : Visual Analogue Scale ; ADE = Adverse Drug Events ; FPNS = Fentanyl Pectin Nasal Spray ; S1 = Session 1

Figure2: Procedure course including outcome measures.



VAS : Visual Analogic Scale ; S1 = Session 1

Table 1: Population characteristics

	Value
Population	
Effective	57 (100)
Age, years	88, 89 [84.0-93.0]
Gender, female	41 (72)
Weight (kg)	64, 62 [55-73]
Mini Mental State Examination* (/30)	20, 22 [16.5-23.7]
Concomitant Antalgic Treatment	
Acetaminophen	54 (95)
Opioids	42 (74)
Fentanyl Indication	
Physiotherapy	45 (79)
Wound dressing	12 (21)
VAS0	
Without FPNS (sessions 1 and 2)	4, 4 [0-6]
With FPNS (sessions 3 to 6)	4, 4 [0-6]
VAS30	
Without FPNS (sessions 1 and 2)	7, 7 [5-8]
With FPNS (sessions 3 to 6)	5, 6 [3-7]
Sessions of care	
Total sessions	314 (100)
Sessions without FPNS	113 (36)
Sessions with FPNS	201 (64)
Sessions with 100µg of FPNS	105 (33)
Sessions with 200µg of FPNS	84 (27)
Sessions with 400µg of FPNS	10 (3)
Sessions with 800µg of FPNS	2 (1)

Data are expressed in numbers (%), means, medians [25-75 percentile]

* : 25-30% Missing data.

PP : Procedural Pain; FPNS : Fentanyl Pectin Nasal Spray; VAS 0 = Visual Analog Scale before FPNS administration; VAS30 = Visual Analog Scale 30 minutes after the FPNS administration

	No FPNS	All dosage	FPNS 100 µg	FPNS 200 µg	FPNS 400µg	FPNS 800µg
Sessions	113	201	105	84	10	2
Sessions with at least one ADE	2 (1.8%)	29 (14.4%)	15 (14.3%)	11 (13.1%)	3 (30.0%)	0
Sessions for Naïve Opioid Patients	30	54	32	19	3	0
Sessions for Naïve Opioid Patients with at least one ADE	MD	7 (13.0%)	3 (9.4%)	2 (10.5%)	2 (66.7%)	0
Sessions for Non-Naïve Opioid Patients	83	147	73	65	7	2
Sessions for Non-Naïve Opioid Patients with at least one ADE	MD	22 (15.0%)	12 (16.4%)	9 (13.8%)	1 (14.3%)	0
Patients	57	57	42	34	8	2
Patients with at least one ADE	2 (3.5%)	27 (47.3%)	13 (31.0%)	11 (32.4%)	3 (37.5%)	0
Ramsey scale	2, 2 [2-2]	2, 2 [2-2]	2, 2 [2-2]	2, 2 [2-2]	2, 2 [2-2]	2, 2 [2-2]
Respiratory scale	0.1, 0 [0-0]	0.1, 0 [0-0]	0.1, 0 [0-0]	0.1, 0 [0-0]	0.2, 0 [0-0]	0, 0 [0-0]
ADE	2	44	24	16	4	0
Vomiting		6 (3.0)	3 (2.9)	2 (2.4)	1 (10.0)	
Nausea	1 (0.9)	6 (3.0)	3 (2.9)	2 (2.4)	1 (10.0)	
Dry mouth		3 (1.5)	2 (1.9)	1 (1.2)	0	
Constipation		2 (1.0)	1 (1.0)	1 (1.2)	0	
Somnolence		9 (4.5)	5 (4.8)	4 (4.8)	0	
Confusion		4 (2.0)	1 (1.0)	3 (3.6)	0	
Dizziness	1 (0.9)	2 (1.0)	2 (1.9)	0	0	
Asthenia		2 (1.0)	1 (1.0)	1 (1.2)	0	
Fall		1 (0.5)	1 (1.0)	0	0	
Anxiety		1 (0.5)	1 (1.0)	0	0	
Hallucination		1 (0.5)	0	1 (1.2)	0	
Insomnia		1 (0.5)	1 (1)	0	0	
Accidental Overdose		3 (1.5)	1 (1)	0	2 (20)	
Cheyne Stroke Respiration		1 (0.5)	1 (1)	0	0	
Respiratory distress		1 (0.5)	0	1 (1.2)	0	
Nocturia		1 (0.5)	1 (1)	0	0	

Data are expressed in numbers (%). Ramsey and Respiratory scales are expressed in means, medians [25-75 percentile]. The detail of adverse events is expressed in numbers and percentage of sessions.
ADE = Adverse Drug Events, FPNS = Fentanyl Pectin Nasal Spray, MD = Missing Data