Reports of Investigation

Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief

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Purpose: To investigate whether the nasal route for fentanyl administration in patient-controlled analgesia (PCA) provides as effective postoperative analgesia as intravenous PCA.

Methods: Patient-controlled intranasal or intravenous analgesia with fentanyl was investigated in 48 patients (ASA I - III) on the day of surgery (orthopedic, abdominal or thyroid) in a prospective, randomized, double-blind, double-dummy study. Fentanyl was given in a bolus of 25 μg for intranasal and 17.5 μg for *iv* PCA, lockout interval six minutes. The first requested dose was doubled in both groups. Pain intensity (101-point numerical rating scale) and vital parameters were observed at 11 measurement points during the 240 min study. Patients were asked for side effects at every measurement point and for their satisfaction at the end of the study by the same investigator (J.M.).

Results: Onset of analgesia, the first reduction in pain intensity on the numerical rating scale, was 21 ± 11 min (range 15 - 45 min) in intranasal and 22 ± 16 min (range 15 - 90 min) in *iv* PCA. Pain intensity was reduced from 55 ± 11 to 11 ± 10 in the intranasal group and from 53 ± 8 to 11 ± 6 in the *iv* PCA group. Vital parameters remained stable and side effects were comparable in both groups. The judgement "excellent" or "good" was given by 21 of 23 patients treated intranasally and 24 of 25 patients treated intravenously.

Conclusion: Intranasal PCA with fentanyl was an effective alternative to *iv* PCA in postoperative patients.

Objectif : Vérifier si l'administration de fentanyl par voie nasale, comme analgésie contrôlée par le patient (ACP), procure une analgésie aussi efficace que l'ACP par voie intraveineuse.

Méthode : L'analgésie contrôlée par le patient, avec du fentanyl par voie intranasale ou intraveineuse, a fait l'objet d'une étude prospective, randomisée, en double aveugle et double feinte, chez 48 patients (ASA I-III), le jour de l'intervention chirurgicale (orthopédique, abdominale ou thyroïdienne). Le fentanyl a été administré en un bolus de 25 μg par voie nasale et de 17,5 μg par voie intraveineuse et la période réfractaire a été de six minutes. La première dose demandée a été doublée chez les patients des deux groupes. L'intensité de la douleur (101 à l'échelle d'estimation numérique) et les paramètres vitaux ont été mesurés à 11 reprises pendant les 240 min de l'étude. C'est le même chercheur (J.M.) qui a interrogé les patients sur les effets secondaires lors de chaque mesure et sur leur satisfaction à la fin de l'étude.

Résultats : Le délai d'installation de l'analgésie, le temps nécessaire à la première réduction de l'intensité de la douleur selon l'échelle d'estimation numérique, a été de 21 ± 11 min (intervalle de 15 - 45 min) pour l'ACP intranasale et de 22 ± 16 min (intervalle de 15 - 90 min) pour l'ACP *iv*. L'intensité de la douleur a été réduite de 55 ± 11 à 11 ± 10 dans le groupe intranasal et de 53 ± 8 à 11 ± 6 dans le groupe *iv*. Les paramètres vitaux sont demeurés stables et les effets secondaires comparables chez les patients des deux groupes. L'analgésie a été jugée «excellente» ou «bonne» par 21 des 23 patients traités avec l'ACP intranasale et par 24 des 25 patients traités avec l'ACP intraveineuse.

Conclusion : L'ACP intranasale avec le fentanyl a été une solution de rechange efficace à l'ACP *iv* en administration postopératoire.

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INTRAVENOUS patient-controlled analgesia (PCA) with an opioid is a widespread therapy for postoperative pain relief.¹ The main advantage of PCA is titration of the analgesic drug according to the patient's individual requirements, thereby maximizing pain relief and minimizing the risk of opioid overdose with subsequent respiratory depression. Intravenous PCA has been shown to provide excellent pain relief and patient satisfaction.² Disadvantages of intravenous PCA are the necessity of intravenous access and a PCA-pump that restricts the patients' mobility. Intranasal PCA (PCINA) has been developed as an alternative delivery mode.^{3,4} There is evidence that PCINA with fentanyl is equivalent to *iv* PCA with respect to pain relief, patient satisfaction and side effects.⁵ However, that study was not double-blind. The present study is the first to compare PCINA with *iv* PCA in a double-blind design.

Methods

After approval by the local Ethics Committee, 57 patients gave written informed consent to take part in this prospective, randomized, double-blind, double-dummy study. Inclusion criteria were age between 18–80 yr, ASA status I, II or III, operation under general anesthesia and postoperative pain intensity > 40 on a 101-point numerical rating scale (NRS; 0 = no pain, 100 = worst pain possible). Exclusion criteria were allergy to opioids, regular medication with analgesic drugs during the four weeks prior to the operation and a previous operation on the nose or nasopharynx. Anesthesia was not standardised. Patients received either 3–5 mg·kg⁻¹ thiopental or 2–2.5 mg·kg⁻¹ propofol for induction of anesthesia. For muscle relaxation 0.08 mg·kg⁻¹ vecuronium or 1 mg·kg⁻¹ succinylcholine was given after pretreatment with 0.01 mg·kg⁻¹ vecuronium for prevention of fasciculations. The lungs were ventilated with oxygen and nitrous oxide in a ratio of 1:2, and anesthesia was maintained with admixture of isoflurane or enflurane according to individual needs. A total of 0.05–0.45 mg fentanyl or 20–50 µg sufentanil was given for intraoperative analgesia. The last intraoperative opioid dose was given at least one hour before tracheal extubation. Patients were randomly allocated postoperatively to either the intranasal or the intravenous group after they had reached a pain intensity > 40 on the NRS. Every patient had both an *iv* PCA device (Abbott Lifecare 4200) and an intranasal PCA device and, when in pain, activated both pumps, one of them contained fentanyl and the other, normal saline. The intranasal PCA pump was a modified Baxter *iv* PCA pump with an adapter for intranasal drug application.⁶

Fentanyl citrate was used in the commercially-available concentration (Fentanyl Janssen®, 1 mL = 0.05 mg). The bolus dose of fentanyl was 17.5 µg in the *iv* group and 25 µg in the intranasal PCA group. The *iv* bolus was 70% of the nasal bolus since systemic bioavailability of fentanyl after nasal application has been reported to be 71%.⁷ The first bolus was doubled in both groups, and the lockout interval was six minutes in both groups. Patients were asked to rate their pain intensity on the NRS every 15 min in the first hour and every 30 min thereafter until four hours after the first PCA request. Sedation was measured using a 5-point scale: 0 = asleep, not arousable, 1 = asleep, arousable on touch, 2 = sedated but responsive, 3 = tired, 4 = fully awake. Patients were removed from the study if they considered pain relief to be insufficient one hour after the PCA treatment had started and were then treated conventionally with on-demand boluses of piritramide *iv*. Blood pressure, respiratory rate, heart rate and arterial hemoglobin oxygen saturation (pulse oximeter BIOX 3740, Ohmeda) as well as side effects were monitored at the same measurement points as pain intensity. Sedation was scored by an observer (J.M.) throughout the study using a numerical scale (0 = asleep, not arousable, 1 = asleep, arousable on touch, 2 = sedated, responsive, 3 = awake, feels tired, 4 = fully awake). At the end of the study, the patients were asked to judge the quality of pain relief using a grading scale as follows: 1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, 5 = very poor, 6 = unacceptable.

Statistical analysis of data

The Mann-Whitney-U-test was used for statistical analysis of differences in pain intensity and vital parameters between groups and the Wilcoxon paired-sample test for differences within each group. Differences between groups concerning patient's sex and type of operation were tested with the Chi-square-test. *P* < 0.05 was considered statistically significant.

Results

The two groups were comparable with regards to demographic data and type of operation (Table I). Forty-eight patients completed the study (23 intranasal PCA / 25 *iv* PCA). Nine of the 57 enrolled patients were removed for the following reasons: insufficient pain relief (4; 2 intranasal, 2 *iv* PCA), pain score < 40 (2), reoperation (1), organizational problem (1), protocol violation (1). No more than 0.2 mg fentanyl was given intraoperatively to 19 of 23 patients in the intranasal PCA group and 22 of 25 patients in the *iv* PCA group. The remaining patients received intraoper-

TABLE I Demographic data and types and duration of operation of the study patients.

	Intranasal PCA (N=23)	iv PCA (N=25)
Age (yr)*	46 ± 15	45 ± 14
Body weight (kg)*	76 ± 14	71 ± 11
Height (cm)*	170 ± 9	167 ± 10
Operation time (min)*	97 ± 46	82 ± 27
Men	11	8
Women	12	17
Abdominal surgery	5	7
Orthopedic surgery	8	10
Thyroidectomy	7	7
Other type of operation	3	1

*Values represent mean ± SD. Differences between groups were not statistically significant (Chi-square-test, Mann-Whitney-U-test).

TABLE II Side effects of patients during intranasal and iv PCA.

	Intranasal PCA	iv PCA
Nausea	5	7
Vomiting	3	5
Irritation of nasal mucosa	1	3
Feeling hot	1	4
Euphoria	0	3
Urinary retention	1	0
Headache	1	0
Dryness of mouth	1	0
Number of patients with side effects / total*	9 / 23	17 / 25

*More than one side effect occurred in some patients.

atively either fentanyl >0.2 mg (2 intranasal group; 1 iv group) or sufentanil (2 intranasal group; 2 iv group). Pain relief was of the same intensity and of comparable speed of onset in both treatment groups. Onset of analgesia was defined as the first reduction in pain intensity on the numerical rating scale. There was no difference in pain intensity between the two groups at any measurement point (Figure 1). Time of onset of pain relief after beginning fentanyl titration was 21 ± 11 min (range 15 – 45 min) in the intranasal and 22 ± 16 min (range 15 – 90 min) in the iv PCA group (mean ± SD). Time to maximum pain relief was 106 ± 67 min (range 15– 240 min) in the intranasal group and 107 ± 47 min (range 15–210 min) in the iv PCA group. The number of PCA requests was comparable in both groups (13.3 ± 6.6 intranasal vs 13.2 ± 5.4 iv PCA; mean ± SD). Vital parameters (heart rate, blood pressure, respiratory rate, arterial hemoglobin oxygen saturation) showed no clinically relevant changes in either group. There was no

FIGURE 1 Pain score on the 101-point numerical rating scale. Closed circles represent intranasal PCA, triangles represent iv PCA (mean ± SD).

difference in sedation score between the groups at any measurement point. The other side effects were also comparable (Table II). Patient satisfaction was high in both groups: the judgement "excellent" or "good" was given by 21 of 23 patients treated with intranasal PCA and 24 of 25 patients treated with iv PCA.

Discussion

The results of this double-blind study confirm the results of previous work³⁻⁵ that intranasal PCA with fentanyl is as effective as iv PCA for the treatment of postoperative pain. Pain relief was effective and of rapid onset in both groups.

Four patients withdrew their consent because of insufficient analgesia 60 min after the beginning of the study period (2 intranasal PCA, 2 iv PCA). Nevertheless, overall satisfaction was high, with 45 of 48 patients considering their pain relief to be good or excellent. None of the patients had difficulty in using the intranasal PCA device and no device failed. Since the systemic bioavailability of fentanyl after application to the nasal mucosa is 71%,⁷ the intravenous dose in this study was reduced to 70% of the nasal dose. This correction for bioavailability explains why patients in both groups made a comparable number of PCA requests (13.3 intranasal PCA vs 13.2 iv PCA). The incidence of nausea (intranasal PCA: 22%, iv PCA: 28%) and vomiting (intranasal PCA: 13%, iv PCA: 20%) is higher in this study than in previous studies^{3,4} (2-5%), but this was true for iv PCA as well as for intranasal PCA. One reason for this high incidence could be extensive question-

FIGURE 2 Patient-controlled intranasal analgesia with a mechanical PCA pump.

ing about this side effect. Nausea and vomiting are common side effects of all opioids. The incidence of nausea and vomiting is reported to be >10% in chronic treatment with transdermal fentanyl.⁸ There were no clinically relevant changes in hemodynamic stability and no signs of respiratory depression in any patient in this study. For clinical use of intranasal PCA it would be ideal to have an electronically-controlled intranasal PCA device with the same safety features as an *iv* PCA pump. Still it should be as small and handy as conventional nasal spray bottles.

In conclusion, intranasal PCA with fentanyl can be an effective noninvasive alternative to *iv* PCA.

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