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Postoperative Pain Management by Intranasal Demand-adapted Fentanyl Titration

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The aim of the present study was to investigate whether intranasal administration of fentanyl allows a demand-adapted postoperative opioid titration. Forty-two patients who had undergone surgery for lumbar intervertebral disk protrusion were included in a prospective randomized double-blind study. When complaining about intense pain, 22 patients received six sprays of fentanyl (0.027 mg) intranasally and 6 ml sodium chloride 0.9% intravenously and 20 patients received six sprays of sodium chloride 0.9% intranasally and 6 ml of a diluted fentanyl solution (0.027 mg) intravenously. In both groups, these doses were repeated every 5 min until the patients were free of pain or refused further analgesic. Before the beginning of opioid titration and then every 10 min for at least 1 h, pain was evaluated with the aid of a 101-point numerical rating scale and a verbal rating scale. Blood pressure, heart rate, arterial hemoglobin oxygen saturation, respiratory rate, and side effects were recorded. All patients were satisfied with the pain reduction achieved. The total fentanyl dose was 0.073 mg (range 0.027–0.162) in the intravenous group and 0.11 mg (range 0.027–0.243) in the intranasal group. The onset of action after intranasal application was nearly as fast as after intravenous titration. The pain reduction achieved was comparable in both groups. Only at the (10-), 20- and 30-min measurement points was the pain intensity significantly lower in the intravenous than in the intranasal group. One patient of the intravenous group showed a decrease in arterial hemoglobin oxygen saturation to less than 90%. Other serious side effects were not observed. Intranasal fentanyl application was well tolerated by all patients. No patient of either group complained about pain or burning in the nose during or after nasal administration. Intranasal administration of fentanyl provides a comfortable way of opioid titration with a rapid onset of action. This mode of administration is suitable for postoperative pain management. (Key words: Analgesics, intranasal: fentanyl. Anesthetic techniques: demand-adapted administration. Pain: postoperative.)

A HIGH PERCENTAGE of patients complain about insufficient postoperative pain relief.[1–4] This is due not to a lack of availability of potent opioids but to often improper administration. Opioids for postoperative pain management are most often given by intramuscular injections.[5,6] Because of the slow onset of action,[7] intramuscular injection requires administration of a predetermined dose and is not suitable for demand-adapted opioid titration. Since there is great interindividual variation in pain perception and opioid requirement,[8] a prefixed dose may represent either an overdose or an underdose for an individual patient. The risk of respiratory depression associated with opioid overdose can be avoided only by demand-adapted opioid titration. This requires a mode of application with a fast onset of pain relief like the intravenous route. Patients in the recovery room still have an intravenous catheter and should therefore receive intravenous opioid titration. In the late postoperative period, when most patients—particularly after extraabdominal surgery—no longer have an intravenous catheter, an alternative mode of opioid administration that also provides rapid onset of action and thus allows opioid titration to individual needs may be required.

It is well known that a systemic effect can be achieved by nasal administration of different substances. For instance, desmopressin, lypressin, gonadorelin, oxytocin, calcitonin, and buserelin are available for intranasal administration in a clinical setting. There have also been some positive results with nasal administration of insulin,[9] propranolol,[10] and testosterone.[11] In a recently published paper, it was shown that children following intranasally administered sufentanil separated more willingly from their parents and cried less frequently. Fewer of them required analgesics in the recovery room.[12]

A pilot study of our group investigating intranasal fentanyl administration for postoperative pain management has yielded encouraging results.[13] The aim of the present study was to investigate whether intranasal fentanyl provides a fast onset of pain relief and allows titration adapted to individual demands. A further question of interest was whether intranasal fentanyl administration is associated with relevant side effects.

Materials and Methods

The present study was approved by the ethical committee of Steglitz Medical Center of the Free University of Berlin. Sixty ASA physical status 1 or 2 patients undergoing surgery for lumbar disc protrusion gave their written consent to participate in this prospective randomized and double-blind study.

Of these patients, only those who complained about intense postoperative pain (greater than 40 on the 101-point numerical rating scale) and accepted an analgesic were finally included in the study. Eighteen patients did

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not fulfill this criterion: in 17 patients the maximum pain intensity was less than 40 on the 101 point numerical rating scale, and in 1 patient the pain intensity exceeded 40, but the patient refused an analgesic. Forty-two patients were finally included in this study. Their data are shown in table I.

All patients received a standardized intramuscular premedication consisting of 50 mg meperidine, 25 mg promethazine, and 0.5 mg atropine. Patients received 1 mg vecuronium for prevention of fasciculation and 0.1 mg fentanyl plus 4 mg/kg thiopental and 1 mg/kg succinylcholine for induction of anesthesia. Anesthesia was maintained with oxygen and nitrous oxide at a ratio of 1:2 and isoflurane according to individual needs. Muscle relaxation was maintained using 7 mg vecuronium.

Patients were randomly allocated to the intravenous or intranasal group. A spray bottle with a premetered spray was used for intranasal application of fentanyl or placebo. One spray corresponded to 0.09 ml. The commercially available fentanyl citrate solution was used for intranasal fentanyl application (1 ml = 0.05 mg fentanyl); a premetered spray of 0.09 ml therefore contained 0.0045 mg fentanyl. For intravenous administration, a fentanyl solution diluted with 0.9% sodium chloride was used; 1 ml of this solution contained 0.0045 mg fentanyl.

The patients of the intranasal group received six sprays of the fentanyl solution (0.027 mg) when complaining about intense postoperative pain. To maintain the double-blind conditions, the patients also received 6 ml sodium chloride 0.9% intravenously. The patients of the intravenous group received 6 ml of the diluted fentanyl solution (0.027 mg) when complaining about intense postoperative pain. To adhere to the double-blind conditions, these patients simultaneously received six sprays of sodium chloride 0.9% intranasally. Each intranasal as well as intravenous dose was given within 25 s. These doses were repeated every 5 min until the patient was free of pain or refused a further analgesic. If demand-adapted intravenous or intranasal fentanyl administration did not provide marked pain relief within 30 min, the patient was excluded from the study and received intravenous piritramide titration. This represents the standard postoperative pain management in our department.

Patients who required further analgesia 60 min after the initiation of intranasal or intravenous fentanyl titration received no additional doses of the short-acting fentanyl. Instead, they received a demand-adapted intravenous titration with the long-acting piritramide in view of their forthcoming transfer to the ward. After the application of piritramide, the patients were likewise excluded from the study.

All patients were monitored for at least 2 h in the recovery room. Monitoring included continuous and noninvasive recording of heart rate (ECG), arterial hemoglobin oxygen saturation (Sp_{O_2}; Nellcor 1000), and respiratory rate. Blood pressure was determined according to Riva-Rocci at 10-min intervals. All patients routinely received 2 l oxygen per minute *via* nasal prongs.

Pain intensity was measured on a 101-point numerical rating scale (0 = no pain, 100 = worst pain possible) and a verbal rating scale (none, mild, moderate, severe, very severe, worst pain possible). These two rating scales were explained to the patients on the day before the operation. Pain intensity was evaluated at 10-min intervals before administration of fentanyl and for at least 60 min after starting fentanyl titration.

At each evaluation, the patients' sedation was also scored by observers' judgment using a grading scale as follows:

1 = alert
2 = drowsy
3 = sleeping; can be awakened by talking to the patient
4 = sleeping; can be awakened by gentle shaking
5 = sleeping deeply; difficulty awakening

The occurrence of any side effects was also documented.

Statistical Analysis of Data

To analyze differences between the two study groups for demographic characteristics, length of surgery, and anesthesia as well as pain intensity evaluated with the 101-point numerical rating scale, the Mann-Whitney U-test for independent samples was used. The differences between the parameters evaluated with the aid of the verbal rating scale were analyzed using the chi-square test. Time-dependent changes within one group were assessed by the Wilcoxon test for matched samples. $P < 0.05$ was considered statistically significant. The results of pain evaluation are presented as median and interquartile range. All other parameters are given as mean ± standard deviation.

TABLE 1. Demographic Characteristics of Both Patient Groups

	Intravenous Group	Intranasal Group	
Male	7	10	
Female	13	12	
Age (yr)	42.9 ± 11.8	45.8 ± 9.7	NS
Weight (kg)	77.4 ± 16.4	72.9 ± 13.2	NS
Height (cm)	172.5 ± 8.3	173.6 ± 10.7	NS
Duration of surgery (min)	76.8 ± 33.4	72.2 ± 26.6	NS
Duration of anesthesia (min)	116.2 ± 48.7	108.8 ± 25.46	NS

NS = difference not significant.

TABLE 2. Postoperative Fentanyl Requirement in the Two Study Groups

	Mean (mg)	Standard Deviation (mg)	Minimal Dose (mg)	Maximal Dose (mg)
Intravenous group (n = 20)	0.073	0.04	0.027	0.162
Intranasal group (n = 22)	0.11	0.06	0.027	0.243

Results

The two groups were similar with respect to age, weight, height, duration of surgery, and anesthesia.

Table 2 shows the amount of fentanyl required by the patients. The patients of the intravenous group required a mean of 0.073 mg fentanyl *versus* 0.11 mg in the intranasal group. There was no need to stop fentanyl titration in any of the patients because of insufficient pain relief.

Initial pain intensity (measurement point zero) did not differ between the two groups (figs. 1 and 2). The postoperative pain scores of both groups determined on the 101-point numerical rating scale are depicted in figure 1. Within 10 min, there was a significant decrease in pain intensity in both groups compared to the initial postoperative pain score (measurement point zero). A significant intergroup difference was found at the 10-, 20-, and 30-min measurement points. Figure 2 depicts the postoperative pain intensity evaluated with the aid of the verbal rating scale in the two groups. Again, both groups showed a significant decrease in pain intensity within 10 min after the initial determination value (measurement point zero) and showed significant intergroup differences at the 20- and 30-min points.

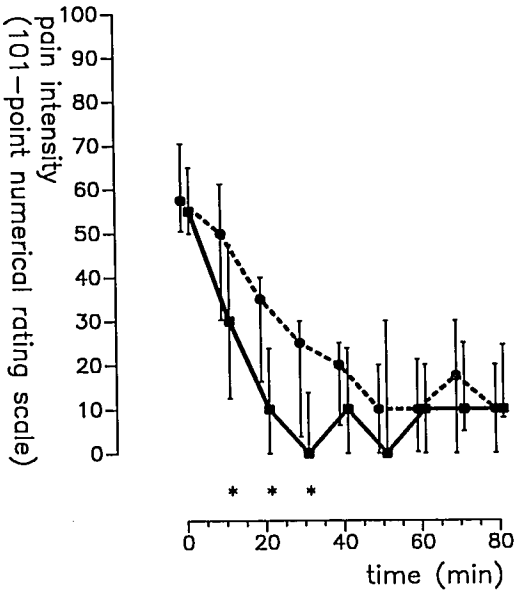

FIG. 1. Postoperative course of pain intensity determined on the 101-point numerical rating scale of both the intranasal (dashed line) and the intravenous (solid line) group (median ± interquartile range). *$P < 0.05$.

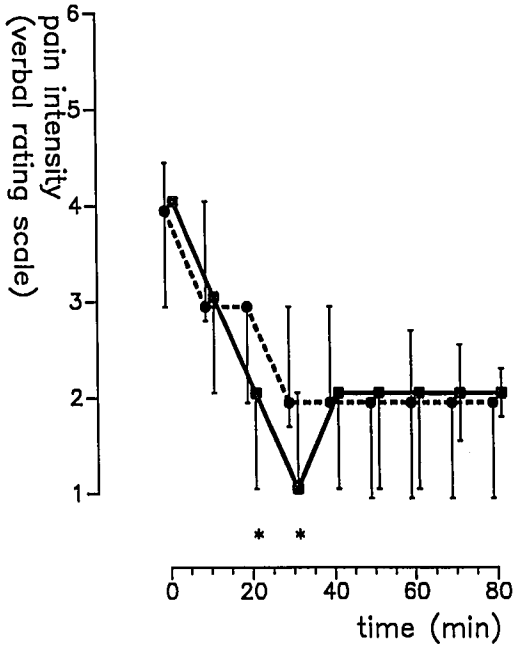

FIG. 2. Postoperative course of pain intensity determined on the verbal rating scale of both the intranasal (dashed line) and the intravenous (solid line) group (1 = no pain; 6 = worst pain possible) (median ± interquartile range). *$P < 0.05$.

In the postoperative course, there was no significant intergroup difference with respect to heart rate and respiratory rate. There was, however, a significant difference between the two groups in systolic blood pressure at the 20-min point, in Sp_{O_2} at the 70-min point, and in the sedation score at the 30-min point (fig. 3). The occurrence of side effects is documented in table 3. The incidence was similar in the two groups.

Discussion

Results from the present study show that intranasal demand-adapted fentanyl titration is as effective as intravenous fentanyl titration for initial treatment of pain following lumbar laminectomy.

The onset of action after intranasal titration was nearly as fast as that after intravenous titration. Furthermore the relatively small intergroup difference in fentanyl dosage in these two homogenous groups (standardized premedication, anesthesia, and surgery) suggests high bioavailability of fentanyl after intranasal administration. The high bioavailability following intranasal administration

results primarily from the entrance of venous blood flow from the nasal mucosa directly into the systemic circulation, thus avoiding the hepatic first-pass effect. Opioids with a high lipid solubility, such as fentanyl (octanol/water partition coefficient of 813), are superior candidates for effective transmucosal absorption compared to opioids with a low lipid solubility, such as morphine (octanol/water partition coefficient of 1.4).[14] Other important factors for effective transmucosal absorption are a high diffusible fraction as well as a high potency of the opioid used.

The pain-relieving effect after intranasal fentanyl occurred nearly as early as that after intravenous administration. A highly significant pain reduction was seen within 10 min (figs. 1 and 2). The rapid onset of action following intranasal administration for premedication has also been described in studies investigating intranasal sufentanil[12,15,16] or midazolam.[17] Both Henderson *et al.*[12] and Vercauteren *et al.*[16] have shown that intranasal sufentanil produced a significant sedative effect within a median of 10 min after administration. Wilton *et al.* demonstrated a dose-dependent calming effect of intranasal midazolam 5 and 10 min after administration.[17] This rapid onset of action following intranasal midazolam application was also confirmed in pharmacokinetic studies by Walbergh *et al.*,[18] who showed that peak plasma concentrations were reached within 10.2 ± 2 min after intranasal midazolam application.

In our study, we saw no clinically relevant changes in

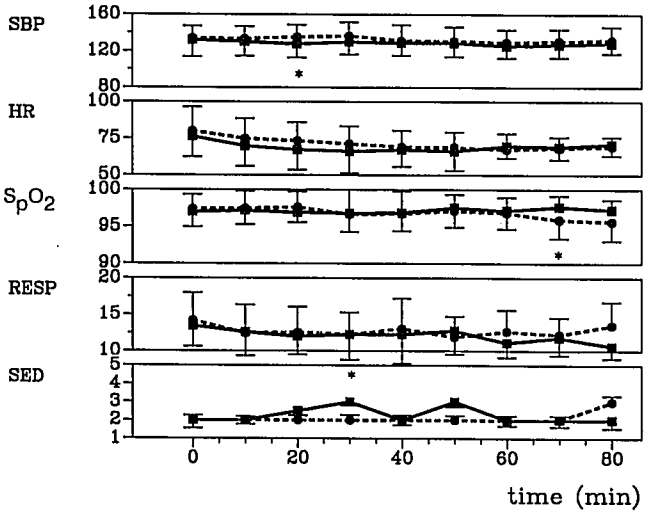

FIG. 3. Postoperative course of systolic blood pressure (SBP; mmHg), heart rate (HR; beats per minute), arterial hemoglobin oxygen saturation (Sp_{O_2}; %), respiratory rate (RESP; breaths per minute), and sedation score (SED; 1 = alert; 5 sleeping deeply, difficulty awakening) of both the intranasal (dashed line) and the intravenous (solid line) group (mean ± SD). *$P < 0.05$.

TABLE 3. Postoperative Side Effects of Fentanyl Titration in the Two Study Groups

Side Effects	Intravenous Group	Intranasal Group
Dizziness	1	1
Nausea	1	0
Vomiting	1	0
Pain or burning in the nose	0	0
Itching	0	0
Euphoria	5	5

postoperative heart rate, systolic blood pressure, Sp_{O_2}, or respiratory frequency compared to the initial values. In one patient of the intravenous group, Sp_{O_2} decreased to less than 90%. This parameter remained greater than 97% after the patient had been asked to take deep breaths. None of the patients in our study complained of pain or burning in the nose. No study in the literature on intranasal application of midazolam, ketamine, or sufentanil mentions damage or irritation of the nasal mucosa.[12,15–17,19,20] In an *in vitro* study investigating the effects of morphine, fentanyl, and sufentanil on ciliary beat frequency of human nasal epithelium, Hermens *et al.* concluded that these drugs have a very low ciliotoxic effect, which is not a contraindication for chronic nasal administration.§

The encouraging results of the present study of postoperative pain management by intranasal opioid application are confirmed by recently published data on intranasal butorphanol.[19] This paper, published in 1991, is as yet the only report by another study group dealing with intranasal opioid administration for pain management. However, to date, no one has performed a strictly demand-adapted intranasal opioid titration.

It is conceivable to construct a special spray bottle providing the same degree of safety measures as a patient-controlled analgesia device (*e.g.*, programmable lock out time, maximum dosage per hour, and size of a bolus). Following the development of such a spray bottle, the patients could perform self-controlled intranasal administration of an opioid.

We think that intranasal fentanyl administration is especially useful in the late postoperative period, when the patients have returned to the general nursing wards for several hours and may not have an intravenous catheter in place. Furthermore, intranasal opioid administration may also be suitable for patients suffering from break-

§ Hermens WAJJ, Schüsler-van Hees MTIW, Merkens FWHM: The in vitro effect of morphine, fentanyl and sufentanil on ciliary beat frequency of human nasal epithelial tissue. Acta Pharm Techno 33: 88, 1987.

through cancer pain or for patients undergoing a painful dressing change.

In conclusion, our randomized prospective and double-blind study of 42 patients under standardized conditions (standardized premedication, anesthesia, and surgery) demonstrated that the pain-relieving effect of intranasal demand-adapted fentanyl titration is comparable to that of intravenous fentanyl titration and that the onset of action is nearly as fast. No patient complained of pain or burning sensations in the nose. Intranasal opioid application offers a new method by which acute and possibly chronic pain may be treated noninvasively.

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