Intranasal Fentanyl for Analgesia in Adults with Acute Renal Colic

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Abstract

Objectives: The usual treatment of pain in acute renal colic is analgesic in intravenous (IV) route. We tried a rapid, non painful, non-invasive route of administration using intranasal fentanyl versus IV standard treatment (non steroidal anti-inflammatory drug (NSAIDs) plus morphine) for the relief of pain in renal colic presenting to an Emergency Department (ED).
Methods: We conducted a prospective non-blinded randomized clinical trial. A sample of 63 adult patients with clinical diagnosis of acute renal colic was included to receive either intravenous morphine (5 mg) plus ketorolac (30 mg) or intranasal fentanyl (3 µg/kg). Pain score were rated by using a 10 cm visual analogue scale at 0,30 and 60 minutes after the treatment. Primary outcome was pain reduction. Secondary outcomes were adverse events and rescue treatment.
Results: Sixty-three patients were enrolled. Thirty patients received nasal fentanyl and thirty-three received intravenous morphine plus ketorolac. Morphine-ketorolac therapy was statistically significant more effective than nasal fentanyl therapy in visual analog scores at 30 minutes: the difference in mean visual analog scale between the two groups was 1.74 cm (95% confidence interval 0.29 to 3.2; P=0.018) at 30 minutes. There were not statistically significant differences between the two groups at 60 minutes. There were no significant differences between the groups with regard to secondary outcomes (adverse events and rescue treatment).
Conclusions: A combination of intravenous morphine plus ketorolac offers pain relief superior to nasal fentanyl treatment for ED patients with acute renal colic.

Sintesi

La colica renale è un dolore acuto invalidante di frequente riscontro in Pronto Soccorso. Il paziente con colica severa (VAS > 7) è spesso agitato e poco collaborante: il reperimento di un accesso venoso oltre che invasivo non è sempre agevole a fronte di una richiesta pressante di analgesia da parte del paziente stesso. L'obiettivo dello studio è di confrontare l'efficacia e gli effetti avversi di un nuovo approccio analgesico di rapida e semplice somministrazione (fentanyl per via endonasale) versus la classica terapia analgesica endovenosa (morfina + ketorolac). Lo studio è prospettico randomizzato. Endpoint primario è la riduzione del dolore (scala VAS) a 30 e 60 minuti. Endpoint secondario sono gli effetti collaterali e la necessità di trattamento analgesico supplementare. I dati dimostrano che entrambi i trattamenti sono efficaci, ma a 30 minuti la terapia endovenosa è più efficace. A 60 minuti vi è equivalenza analgesica. Non vi sono differenze statisticamente significative sugli endpoint secondari. I risultati di tale lavoro confermano la validità analgesica, la semplicità d'uso e la sicurezza della somministrazione di fentanyl per via endonasale ma l'associazione di ketorolac e morfina per via endovenosa genera un'analgesia più rapida ed efficace.

Introduction

Up to 12 percent of the population will have a urinary stone during their lifetime and recurrence rates approach 50 percent (1). The classic presentation of a renal stone is acute, colicky flank pain radiating to the groin. In the Emergency Department (ED), initial management of renal colic is based on rational and fast diagnostic process, rapid and effective pain control. The main drugs used for treatment of pain in acute renal colic are ketorolac and morphine in IV route. For the treatment of severe pain is useful to combine non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (2-5).
There has not been a study comparing a nasal opiate with an analgesic in the intravenous (IV) route. It is routine in many hospital to give IV analgesics to adults presenting to the ED in moderate to severe pain. However, the insertion of a IV cannula is not always easy in the agitated patient suffering for renal colic. New alternative methods of providing safe and effective analgesia in patients with trauma and burns include the nasal route for the administration of opiates such as fentanyl.
The primary aim of the study was to determine whether intranasal fentanyl alone is equivalent in analgesic effect to IV morphine and ketorolac in patients presenting to the emergency room with acute renal colic. Primary outcome was pain reduction. Secondary outcomes were the need for rescue analgesia at 30 minutes and adverse effects.

Materials and methods

Study Design

This study was a prospectic non-blinded randomized trial. We obtained institutional review board approval. Patients signed informed consent.

Study Setting and Population

The patients were adults aged 18 to 65 years, presenting in ED with classical clinical symptoms of renal colic (sudden monolateral flank pain with inguinal irradiation) with a 10-cm visual analog scale (VAS) greater than or equal to 7. Exclusion criteria were analgesia within 6 hours of arrival, allergy to opiates and NSAIDs, opiates abuse, known or suspected abdominal aortic dissection or aneurism, presence of peritonitis, hemodynamic instability, pregnancy, breastfeeding, anticoagulant therapy. Patients with known renal, pulmonary, cardiac or hepatic failure, as well as those with renal transplantation, were also excluded.

Study Protocol

Patients were randomized in a 1:1 ratio to receive either intranasal fentanyl or morphine-ketorolac treatment in a non-blinded fashion. Treatment allocation assignments were contained in sealed envelope. The randomization schedule was prepared by assistant blinded to the study. After enrollment, every patients was shown a 10-cm with marked numbers visual analog scale and invited to mark the level of pain. Patients were excluded if their pain score fell below 7. Available in all hospitals, concentrated fentanyl citrate (Fentanest 100 µg/2 ml; Pfizer Italia Srl) was used at the dose of 3 µg/kg (doses were based on weight intervals of 10 kg) in intranasal route using the nasal atomizer (MAD device; Wolfe Tory Medical,Salt Lake City, UT). The total volume was divided on 3 doses at time 0,5,and 10 minutes because endonasal maximum dose were 2 ml every 5 minutes (1 ml per nostril). 0.5 ml ampoule of morphine (Morfina cloridrato 10 mg/ml; Molteni & C.; Italy) diluted in saline solution 100 ml followed by 2 ml ampoule of ketorolac (Lixidol 30 mg/2 ml; Roche SpA; Italy) in saline solution 100 ml was infused: total time of infusion 10 minutes. Additional doses could be given after 30 minutes with IV 5 mg of morphine in IV group or intranasal 1.5 µg/kg of fentanyl in intranasal group if requested by the patients. If pain relief was inadequate after 60 minutes, then analgesia in the form of IV morphine or NSAIDs was offered to the patients (on request). During the study period, clinical observations were documented by the attending physician or nurse through monitoring clinical symptoms: the pain intensity score were written by physicians on a separate sheet paper. The time count begins after the administration of the last doses.
Subjects reported pain intensity on both a 10 cm visual analogue scale immediately before receiving the study drug and at 30 and 60 minutes after drug administration. When adverse effects occurred, there were documented by the attending physician or nurse: in particular they are asked to document ventilation failure (respiratory rate < 12/min and/or hypoxiemia), arterial systolic pressure < 100 mmHg, nausea, vomiting, dizziness, drowsiness. We also collected subject demographic information, urinary stone disease and confirmatory diagnostic tests.

Measures

Our primary outcome was the change in visual analogue scale pain intensity score at 30 and 60 minutes. This measure was obtained using a 10-cm with marked numbers visual analog scale. There is evidence in the literature that minimum clinically significant difference in pain scores on visual analogue scale is 1,3 cm (6,7). Secondary outcomes were the occurrence of adverse events and use of rescue therapy.

Data Analysis

A minimum of 29 patients in each group would be required to detect a 1,3 cm difference between groups, assuming an SD of 15 mm, 90% power and a 05 2-sided level of significance. All statistical analyses were performed with SPSS software (version 12.0; SPSS Inc., Chicago, IL).Our primary comparison, the mean between-group change in visual analogue scale pain intensity score at 30 and 60 minutes, was tested with analysis of variance. Rescue therapy was analysed with Fisher exact test. All tests of significance were two sided.

Results

During the 9-month study period, 153 consecutive patients were assessed for elegibility for enrollement in the study and 65 patients were randomized to one of the 2 treatment arms. Eighty-eight patients were inelegible for enrollement in the study (Fig. 1). There were 2 protocol violations (two patients claimed therapy immediately): the patients received rescue therapy before 30 minutes or additional drugs for intractable pain during the observation. We analized 63 patients.

Table 1. Baseline Characteristics of the Patients*.

Characteristics	Fentanyl Group (N=30)	Morphine plus ketorolac Group (N=33)	P value
Age - yr §	40±10	45±10	NS
Body weight*(kg)	67	68	NS
Male sex – no. (%)	17 (56)	18 (54)	–
Initial VAS - cm§	8.8 (±1.5)	8.6 (±1.5)	NS
History of urolithiasis, no.(%)	19 (63)	19 (57)	–
Positive ultrasonography, no. (%)	25 (83)	24 (73)	NS
Hydronephrosis, no(%)	10 (33)	9 (27)	–
Urolithiasis, no. (%)	15 (50)	15 (45)	
Urine analysis positive	25 (85)	27 (82)	–
blood - no. (%)			

§ Plus-minus values are means ± SD. * Mean

Table 2. Adverse effects and rescue treatment.

Characteristics	Fentanyl Group (N=30)	Morphine plus ketorolac Group (N=33)	P value
Adverse effects - no. (%)	5 (16)	5 (15)	0.13
Dizziness	4	3	–
Nausea	1	2	–
Allergic reaction	0	0	–
Arterial hypotension	0	0	–
Respiratory depression	0	0	–
Rescue analgesia at 30 minutes - no. (%)	10 (33)	4 (12)	0.07

The two groups appeared to be similar in the baseline characteristics (Table 1). Mean age of patients was 42 years. Fifthy-five percent were men. Baseline mean VAS score was 8.8 cm in fentanyl group and 8.6 cm in morphine-ketorolac group. All patients had a urinary ultrasound: fourty-five patients (71%) had urolithiasis and/or hydronephrosis. Urine dipstick test was positive for blood in 52 patients (82%). No patient had both negative ultrasound test and negative urine dipstick test.
Age, sex and initial pain score had no impact on pain reduction. The VAS score at baseline, 30 minutes and 60 minutes are illustrated in Fig. 2. The mean reduction in VAS scores at 60 minutes was 6.6 cm for fentanyl and 7.6 cm for morphine and ketorolac. The analysis of variance showed statistically significant differences in visual analog scale between the ketorolac-morphine group and fentanyl group at 30 minutes in favour of morphine and ketorolac (P = 0.017). At 60 minutes, the difference between the two groups was not statistically significant although the trend was in favour of morphine and ketorolac combination. Also we compared the performance of the VAS score of fentanyl (VAS baseline versus VAS 30 min versus VAS 60 minutes), we found statistically significant differences (P < 0.0001 at 30 minutes and P = 0.023 at 60 minutes); also in morphine and ketorolac group VAS score at baseline compared with VAS 30 and 60 minutes showed statistically significant differences (P<0.0001 at 30 minutes and P=0.019 at 60 minutes). In both groups the greatest effect occurred within the first 30 minutes: mean reduction of VAS score at 30 minutes was 54% for fentanyl group and 74% for combination group. Total mean reduction of VAS score was 75% for fentanyl group and 87% for combination group.
The mean time from the diagnosis of acute renal colic to first treatment was within ten minutes (mean time 9.7 min, range 5-18 min).
There were no significant differences between the groups with regard to adverse events: five patients (16%) in fentanyl group and five patients (15%) in the combination group. All adverse events were mild, transient and well tolerated by patients.
Fourteen of 63 patients (22%) required rescue therapy at 30 minutes for adequate pain relief: four of 33 (12%) in the morphine-ketorolac group and ten of 30 (33%) in the fentanyl group. However, this result was not significantly different (2.75;95% CI 0.97 to 7.84, P=0.068). There was a negative trend of rescue treatment for fentanyl group compared with morphine and ketorolac group.
The adverse events and rescue analgesia are illustrated in Table 2.

Discussion

Intranasal drug administration has been studied widely in postoperative patients (8-10), in burn patients (11-13) and in pediatric patients successfully (14-16). The aim of this study was to find a rapid, non invasive and effective therapy. This study is the first to compare directly intranasal fentanyl with intravenous therapy in acute renal colic: usually we use a standard

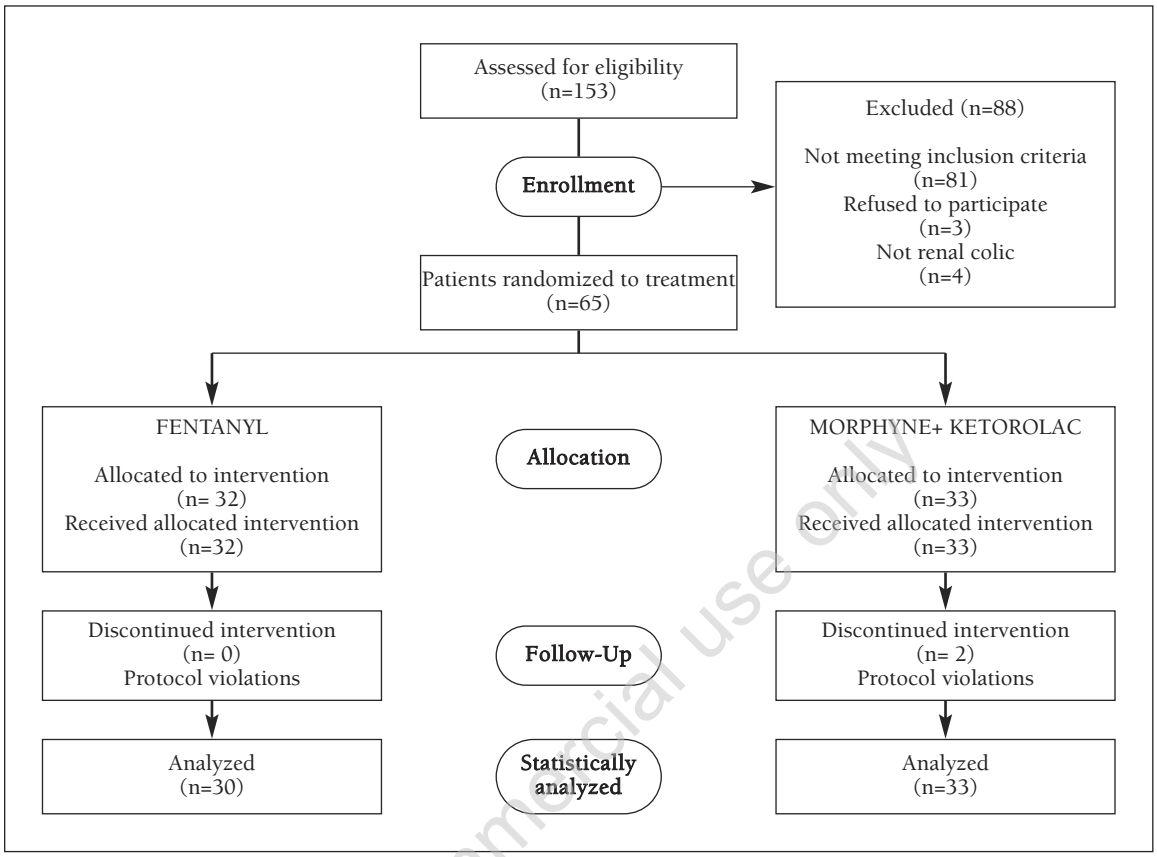
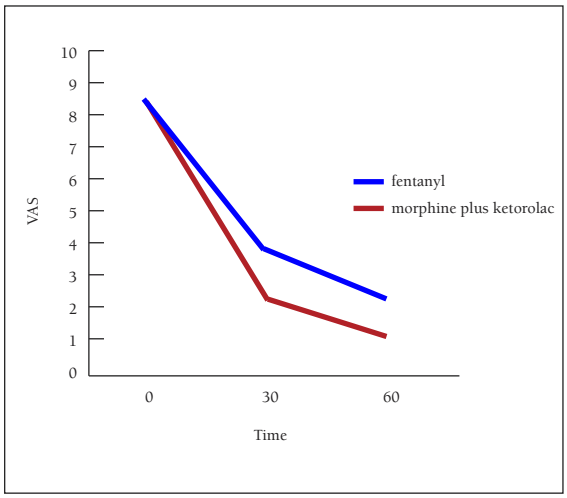


Fig. 1. Flow chart.

opioid with NSAIDs for moderate-severe pain because the combination of the two drugs was synergistic and appeares to be more effective with fewer side effects than single drug at higher doses (5). Also we used comparable US Food and Drug Administration – approved doses of each drug (ketorolac 15-30 mg iv and morphine 0.1 mg/kg iv) (17). The visual analog scale score showed a significant reduction for both treatment arms but morphine and ketorolac was significant superior to fentanyl at 30 minutes. Although intranasal fentanyl has been shown to have therapeutic serum levels in 2 minutes, with a rapid bioavailability (16) and in the clinical setting fentanyl can be administrated promptly into nasal cavity without the delays inherent in placing an IV, our results showed significant difference at 30 minutes in comparison to combination intravenous group. At 60 minutes both treatment were efficacy without clinically difference. These results emphasize the findings of previous trials on efficacy of fentanyl (13-15), but during acute renal colic is important to obtain the more analgesic effect in the first minutes, so we consider that intravenous drug association is preferable than intranasal fentanyl even if latter is more simple and not invasive. Intranasal fentanyl may have a potential in treatment of acute renal colic out of hospital or in a nurse-initiated analgesic in the ED.
In our study there are no significant adverse effects in both treatments: tolerability and acceptability were excellent. Moreover rescue analgesia is not statistically significant different between the two groups.

Limitations

The study contained some limitations.
First, the absence of NSAIDs in the fentanyl group might weaken the powerful of our study but our aim was using a non invasive route of administration. The use of intranasal administration of ketorolac tromethamine has been approved by FDA only recently when the work had been completed. The addition of an oral NSAID would have strenghthened the study and should be considered in future investigations.



	0 min	30 min	60 min
Morphine (cm)	8.6	2.3	1.1
Fentanyl (cm)	8.8	4.0	2.2
Difference (95% CI)	0.18 (-0.4 to 0.76)	1.74 (0.29 to3.2)	1.1 (0 to 2.2)
P	0.018	0.06	–

Fig. 2. Mean pain score over time.

Second, we used 3 µ/kg of nasal fentanyl based on previous studies (13-15). Higher doses of fentanyl could be used but with more side effects. Moreover we used rescue therapy composed with half dose of fentanyl and half dose of combination group (only IV morphine instead of IV morphine + NSAIDs).
Third, SPID (Summed Pain Intensity Difference) and TOTPAR (Total Pain Relief) scores have greater sensitivity to find differences in efficacy than VAS scale but we used it because it was more easy to refer to the patients with acute renal colic (18).
Although morphine is a reasonable initial treatment for renal colic, fentanyl via the IV route has a more rapid onset than morphine and probably would have been a better control of symptoms. Furthermore, our dose of IV morphine was less than 0,1 mg/kg and could be considered an inadequate dose. However, this fact would actually bias our results against the IV morphine and ketorolac group.
Finally, the study was not blinded.

Conclusions

In summary, in this randomized trial intranasal fentanyl as monotherapy was less effective at 30 minutes than morphine and ketorolac together, with a trend towards requiring more rescue analgesia. We therefore consider intravenous morphine and ketorolac to be the first choice for analgesia in patients with acute renal colic in the ED. Further studies should focus on demonstrating the effectiveness of intranasal fentanyl in this and other patient sub-group and eventually at different high doses or in combination with nasal ketorolac.

References

1. Sierakowski R, Finlayson B, Landes RR *et al. The frequency of urolithiasis in hospital discharge diagnoses in the United States.* Invest Urol 1978; 15: 438-41.
2. Holdgate A, Pollock T. *Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic.* Cochrane Database Syst Rev 2004; 1: CD004137.
3. Smally AJ. *Analgesia in renal colic.* Ann Emerg Med 1997; 29: 297-9.
4. Labrecque M, Dostaler LP, Rousselle R *et al. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic: a meta-analysis.* Arch Intern Med 1994; 154: 1381-7.
5. Safdar B, Degutis LC, Landry K *et al. Intravenous morphine plus ketorolac is superior to either drugs alone for treatment of acute renal colic.* Ann Emerg Med 2006; 48: 173-81.
6. Todd KH. *Clinical versus statistical significance in the assessment of pain relief.* Ann Emerg Med 1996; 27: 439-41.
7. Gallagher EJ, Liebman M, Bijur PE. *Prospective validation of clinically important changes in pain severity measured on a visual analogue scale.* Ann Emerg Med 2001; 38: 633-8.
8. Holdgate A, Asha S, Craig J *et al. Comparison of a verbal numeric rating scale with the VAS for the measurement of acute pain.* Emerg Med (Fremantle) 2003; 15: 441-6.
9. Paech MJ, Lim CB, Banks SL *et al. A new formulation of nasal fentanyl spray for post-operative analgesia: a pilot study.* Anaesthesia 2003; 58: 740-4.
10. Wong P, Chadwich FD, Karovitis J. *Intranasal fentanyl for postoperative analgesia after elective cesarian section.* Anaesthesia 2003; 58: 818-9.
11. Galinkin JL, Fazi LM, Cuy RM *et al. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia.* Anesthesiology 2003; 93: 1378-83.
12. O'Neil G, Paech M, Wood F. *Preliminary clinical use of a patient controlled intranasal analgesia (PCINA) device.* Anaesth Intensive Care 1997; 25: 408-412.
13. Finn J, Wright J, Fong J *et al. A randomised crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns.* Burns 2004; 30: 262-8.

14. Borland M, Jacobs I, King B *et al. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the Emergency Department.* Ann Emerg Med 2007; 49: 335-40.
15. Borland M, Jacobs I, Geelhoed G. *Intranasal fentanyl reduces acute pain in children in the Emergency Department: a safety and efficacy study.* Emerg Med 2002; 14: 275-80.
16. Borland M, Bergesio R, Pascoe EM *et al. Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study.* Burns 2005; 31: 831-7.
17. Lacy CF, Goldman MP. *Drug Information Handbook, 12th ed.* Lexington Comp Inc., Hudson OH, 2003.
18. Cooper SA. *Advances in Pain Research and Therapy*. New York Raven Press 1991; 18: 117-24.