Fentanyl sublingual is not inferior to Fentanyl intravenous for acute trauma pain - a prospective, gender-balanced, randomized, double-blind, clinical, single-center noninferiority trial

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Introduction

Ideally acute pain management should provide rapid and adequate pain control without high resource utilisation and major adverse drug reactions. Prospective randomised controlled trials in the emergency setting comparing intravenous and sublingual administration of fentanyl regarding efficacy and safety and gender differences are lacking. Fentanyl sublingual (FSL) is well established in the management of breakthrough cancer pain in nonopioid naïve patients and is favourable to other fentanyl formulations such as fentanyl buccal tablets or fentanyl intranasal spray regarding ease of administration, acceptability, palatability and overall impression. The aim of this study was to compare FSL and Fentanyl intravenous (FIV) for acute moderate to severe trauma extremity pain in emergency medicine in gender-balanced groups.

Methods

This is a prospective, randomised, double-blind, double-dummy, single-centre, non-inferiority clinical trial. 108 adults (54 females and 54 males, ASA I-II) with acute trauma pain ≥ 4 on the 11 points Numeric Rating Scale (NRS) were enrolled in the emergency department of the Regional Hospital in Bruneck, Italy. Patients received either FIV (1 $\mu\text{g kg}^{-1}$) or FSL (100 μg) and the correspondent placebo (Figure 1). Pain was measured before and 5, 10, 20, 30 and 60 minute intervals after administration of the study drug during the entire diagnostic and therapeutic procedure. For insufficient pain relief a rescue medication with 1 $\mu\text{g kg}^{-1}$ fentanyl intravenously at the earliest after 10 minutes was allowed. Other analgesics were not allowed.

Figure 1. Consort Flow Diagram

Results

54 patients (27 females and 27 males) were randomised to each group. Baseline pain intensity did not differ between the therapies, nor between females and males. The 95% confidence interval (CI) of mean difference between FSL and FIV did not include the 1 point non-inferiority margin at any timepoint showing non-inferiority of FSL in pain reduction compared to FIV for the whole observation period (Figure 2). Table 1 shows how many patients reached pain reduction of 2 points on NRS at every timepoint. There was no difference between FSL and FIV groups, and there was no difference between male and female patients. One or more adverse drug reactions (ADR) were present in 51/97 patients [14/46 (30.4%) in the FSL group and 37/51 (72.5%) in the FIV group, $p<0.001$] without rescue dose.

Rescue Dose	Time-point	Fentanyl sublingual				Fentanyl intravenous			
		Female	Male	P-value	Female	Male	P-value		
No	5 min	Patients with 2 patients with 2 reduction reduction	n %	n %	n %	Patients with 2 patients with 2 reduction reduction	n %	n %	n %
	10 min	27 48.1%	10 27 37.0%	0.583	15 27 55.6%	13 27 48.1%	0.786		
	20 min	27 74.1%	18 27 66.7%	0.786	23 27 85.2%	19 27 70.4%	0.327		
	30 min	28 84.6%	21 27 77.8%	0.728	28 27 96.3%	23 26 88.5%	0.351		
	60 min	24 83.3%	21 23 91.3%	0.686	25 27 92.6%	24 26 92.3%	1.000		
Yes	60 min	21 91.3%	22 23 95.7%	1.000	25 100.0%	21 25 84.0%	0.11		
	20 min	0 1 0.0%	- - -	-	- - -	- - -	-		
	30 min	3 100.0%	4 4 100.0%	-	- - -	0 1 0.0%	-		
	60 min	4 100.0%	4 4 100.0%	-	2 2 100.0%	1 1 100.0%	-		

Table 1. Differences for female and male patients with reduction of Numeric Rating Scale (NRS) by 2 points from baseline per therapy timepoint and rescue dose.

Rescue dose	Parameter	Fentanyl sublingual				Fentanyl intravenous			
		Female	Male	P-value	Female	Male	P-value	Female	Male
No	n	23	23		25	25		25	25
	Pain reduction in 60 minutes ^a	7 (30.4%)	7 (30.4%)	0.585	7 (28.0%)	7 (28.0%)	0.981	7 (28.0%)	7 (28.0%)
	Dizziness, n (%)	4 (17.4%)	4 (17.4%)	1.000	19 (76.0%)	14 (56.0%)	0.144	19 (76.0%)	14 (56.0%)
	Nausea or vomiting, n (%)	1 (4.3%)	1 (4.3%)	1.000	3 (12.0%)	1 (4.0%)	0.390	3 (12.0%)	1 (4.0%)
	Pruritus, n (%)	0 (0.0%)	1 (4.3%)	1.000	1 (4.0%)	0 (0.0%)	0.490	1 (4.0%)	0 (0.0%)
	Dry mouth, n (%)	4 (17.4%)	3 (13.0%)	0.820	0 (0.0%)	4 (16.0%)	0.490	0 (0.0%)	4 (16.0%)
	Sedation, n (%)	3 (13.0%)	1 (4.3%)	0.658	2 (8.0%)	3 (12.0%)	0.713	2 (8.0%)	3 (12.0%)
	Participants with at least one side effect, n (%)	8 (34.8%)	6 (26.1%)	0.740	21 (84.0%)	18 (72.0%)	0.116	21 (84.0%)	18 (72.0%)
	Patient "satisfied" or "highly satisfied" t, n (%)	20 (87.0%)	23 (100.0%)	0.233	23 (92.0%)	24 (96.0%)	1.000	23 (92.0%)	24 (96.0%)
	Patient "satisfied" or "highly satisfied" t, n (%)	18 (78.3%)	21 (91.3%)	0.414	25 (100.0%)	23 (92.0%)	0.235	25 (100.0%)	23 (92.0%)
	Investigator "satisfied" or "highly satisfied" (practicability) t, n (%)	22 (95.7%)	23 (100.0%)	1.000	25 (100.0%)	25 (100.0%)	-	25 (100.0%)	25 (100.0%)
Yes	n	4	4		2	2		2	2
	Pain reduction in 60 minutes ^a	0 (0.0%)	0 (0.0%)	0.585	0 (0.0%)	0 (0.0%)	0.327	0 (0.0%)	0 (0.0%)
	Dizziness, n (%)	2 (50.0%)	2 (50.0%)	1.000	1 (50.0%)	0 (0.0%)	1.000	1 (50.0%)	0 (0.0%)
	Nausea or vomiting, n (%)	0 (0.0%)	1 (25.0%)	1.000	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Pruritus, n (%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)
	Dry mouth, n (%)	1 (25.0%)	1 (25.0%)	1.000	1 (50.0%)	0 (0.0%)	1.000	1 (50.0%)	0 (0.0%)
	Sedation, n (%)	1 (25.0%)	0 (0.0%)	1.000	1 (50.0%)	1 (50.0%)	1.000	1 (50.0%)	1 (50.0%)
	Participants with at least one side effect, n (%)	4 (100.0%)	3 (75.0%)	1.000	2 (100.0%)	1 (50.0%)	-	2 (100.0%)	1 (50.0%)
	Patient "satisfied" or "highly satisfied" t, n (%)	3 (75.0%)	4 (100.0%)	1.000	2 (100.0%)	0 (0.0%)	0.333	2 (100.0%)	0 (0.0%)
	Investigator "satisfied" or "highly satisfied" (practicability) t, n (%)	2 (50.0%)	4 (100.0%)	0.449	2 (100.0%)	1 (50.0%)	-	2 (100.0%)	1 (50.0%)
	Investigator "satisfied" or "highly satisfied" (practicability) t, n (%)	4 (100.0%)	3 (75.0%)	1.000	2 (100.0%)	0 (0.0%)	0.333	2 (100.0%)	0 (0.0%)

Table 2. pain reduction, side effects, patient satisfaction and investigator satisfaction per gender. Numbers are presented as mean±standard deviation except where n (%) is specified, which denotes number of cases and percentages.

Dizziness was the most frequent ADR and was reported by 47/108 (43.5%) patients. For all other ADRs there were no differences between the treatment groups and between female and male patients (Table 2).

Conclusion

FSL may be an efficient and safe alternative to FIV for acute moderate to severe trauma pain without differences between female and male patients also in terms of ADRs. More studies are needed to investigate FSL in a larger population and with repeated doses.

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Figure 2. Non-inferiority analysis of mean Numeric Rating Scale (NRS) decrease from baseline of Fentanyl sublingual compared to Fentanyl intravenous. Error bars indicate 2-sided 95% confidence intervals and the vertical dashed black line represents the non-inferiority margin. (A) All patients are included until a rescue dose is administered (as-treated analysis). (B) For every timepoint following the administration of the rescue dose the NRS score considered is the last one before the administration (intention-to-treat analysis).

References

Park CL et al. Prehospital analgesia: systematic review of evidence. J R Army Med Corps. 2010;156(4 Suppl 1): 295-300. Brant JM et al. Breakthrough Cancer Pain: A Systematic Review of Pharmacologic Management. Clin J Oncol Nurs. 2017;21(3 Suppl):71-80. DOI: 10.1188/17.CJON.S3.71-80

Schug SA, Ting S. Fentanyl Formulations in the Management of Pain: An Update. Drugs. 2017;77(7):747-63. DOI: 10.1007/s40265-017-0727-z.

Cepeda MS et al. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther. 2003;74(2):102-12. DOI: 10.1016/S0009-9236(03)00152-8