

# An open-label randomised controlled trial on the efficacy of adding intranasal fentanyl to intravenous tramadol in patients with moderate to severe pain following acute musculoskeletal injuries

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**INTRODUCTION** The use of intranasal fentanyl as an alternative type of analgesia has been shown to be effective in paediatric populations and prehospital settings. There are a limited number of studies on the use of intranasal fentanyl in adult patients in emergency settings.

**METHODS** An open-label study was conducted to evaluate the effectiveness of the addition of 1.5 mcg/kg intranasal fentanyl to 2 mg/kg intravenous tramadol (fentanyl + tramadol arm, n = 10) as compared to the administration of 2 mg/kg intravenous tramadol alone (tramadol-only arm, n = 10) in adult patients with moderate to severe pain due to acute musculoskeletal injuries.

**RESULTS** When analysed using the independent *t*-test, the difference between the mean visual analogue scale scores pre-intervention and ten minutes post-intervention was  $29.8 \pm 8.4$  mm in the fentanyl + tramadol arm and  $19.6 \pm 9.7$  mm in the tramadol-only arm ( $t[18] = 2.515$ ,  $p = 0.022$ , 95% confidence interval 1.68–18.72 mm). A statistically significant, albeit transient, reduction in the ten-minute post-intervention mean arterial pressure was noted in the fentanyl + tramadol arm as compared to the tramadol-only arm (13.35 mmHg vs. 7.65 mmHg; using Mann-Whitney *U* test with *U*-value 21.5,  $p = 0.029$ ,  $r = 0.48$ ). There was a higher incidence of transient dizziness ten minutes after intervention among the patients in the fentanyl + tramadol arm.

**CONCLUSION** Although effective, intranasal fentanyl may not be appropriate for routine use in adult patients, as it could result in a significant reduction in blood pressure.

Keywords: fentanyl, intranasal drug administration, tramadol

## INTRODUCTION

Although pain is a common presentation in emergency departments (EDs),<sup>(1)</sup> lack of pain control or 'oligoanalgesia' frequently occurs.<sup>(2)</sup> In a crowded ED, time to analgesia is often prolonged<sup>(3)</sup> and this can be detrimental, as the quality of pain management affects patient outcomes.

One of the factors that improves the timing of pain management is the route of analgesia administration. Occasionally, clinicians may have difficulty in establishing an intravenous line, resulting in a delay in drug administration. Administering analgesia via the intranasal route has recently been advocated as an alternative method to overcome the problem of delayed drug administration.<sup>(4)</sup> In properly selected patients, use of the intranasal route reduces the time from drug administration to the onset of drug action. It can also help to alleviate manpower constraints and eliminate needlestick exposure risk and injection pain, compared to drug administration via injections.<sup>(5)</sup> The intranasal route enables rapid absorption of the administered drug because the nasal mucosa is highly vascularised; only two cell layers separate the nasal lumen from the nasal mucosa's blood vascular system.<sup>(6)</sup> Furthermore, this route affords a large surface area ( $150\text{--}180\text{ m}^2$ )<sup>(7)</sup> for drug delivery and eliminates first-pass metabolism,<sup>(8)</sup> allowing the drug to enter the cerebrospinal fluid via the olfactory mucosa for

immediate therapeutic effect.<sup>(9)</sup> For example, intranasal fentanyl has been shown to achieve therapeutic serum levels within two minutes of administration.<sup>(10)</sup>

Tramadol, a synthetic opioid of the aminocyclohexanol group, has been shown to possess an analgesic potency equivalent to that of pethidine.<sup>(11)</sup> Fentanyl is a synthetic phenylpiperidine derivative whose analgesic potency is 50–80 times that of morphine.<sup>(12)</sup> Fentanyl also has a rapid onset of action (within 6–8 minutes following intranasal administration) due to its high lipid solubility.<sup>(13)</sup> Studies conducted in prehospital settings have shown that intranasal fentanyl is as effective an analgesic as intravenous morphine in adult<sup>(14)</sup> and paediatric patients.<sup>(15)</sup>

Although the evidence regarding the use of intranasal fentanyl in EDs is limited, the few published studies show promising results. In one study, intranasal fentanyl was shown to be as effective an analgesic as intramuscular morphine in children presenting to the ED.<sup>(16)</sup> In another study conducted in an ED setting, intranasal fentanyl was shown to be comparable to intravenous morphine in reducing pain in a paediatric population that had acute long bone fractures.<sup>(17)</sup> Yet another study showed that it provides effective analgesia for paediatric patients with painful orthopaedic traumas.<sup>(18)</sup> While the use of intranasal fentanyl in the ED has been shown to be effective in paediatric populations,<sup>(9)</sup> there are

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