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A randomised crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns

Judith Finn [a,*], Jan Wright [b], Joy Fong [b], Eileen Mackenzie [a], Fiona Wood [b], Gavin Leslie [c], Anna Gelavis [d]

[a] *The School of Population Health (M431), The University of Western Australia, 35 Stirling Highway, Perth, 6009 WA, Australia*
[b] *Burns Unit, Royal Perth Hospital, Perth, WA, Australia*
[c] *Edith Cowan University/Royal Perth Hospital, Perth, WA, Australia*
[d] *Pharmacy Department, Royal Perth Hospital, Perth, WA, Australia*

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Abstract

This study sought to compare the analgesic efficacy and safety of patient controlled intra-nasal (PCIN) fentanyl with oral morphine for procedural wound care in burns patients. A randomised double-blind placebo controlled, two period, two-treatment crossover trial was conducted within the Burns Unit of a major teaching hospital in Perth, Western Australia. Patients requiring identical wound care procedures on two consecutive mornings (and not prescribed intravenous analgesia) were randomised to receive either PCIN fentanyl with oral placebo or oral morphine with intranasal placebo on 1 day, followed by the alternate active drug on the following day.

Twenty-six patients (22 males), aged between 18 and 69 years (35.5 ± 12.4 years), with total body surface burns (TBSA) range 1–25% ($6.9 \pm 4.5\%$), indicated their level of pain on a 10 point (0–10) numeric scale at various time periods before, during and after the procedure. A mean total dose of $1.48 \pm 0.57\,\mu g/kg$ of PCIN fentanyl and 0.35 ± 0.12 mg/kg of oral morphine was administered. No statistically significant difference was found between the pain scores recorded for patients *during* the procedure with PCIN fentanyl compared to that with oral morphine (mean difference $= -0.75$, 95% CI $= -1.97$ to 0.47, $P = 0.22$). Two patients experienced hypotension during the procedure—both had received active oral morphine. No patients experienced respiratory depression or a significant drop in oxygen saturation. There were four episodes (in three patients) where 'rescue analgesia' for severe pain was required – two episodes involving oral morphine and two involving PCIN fentanyl. It was concluded that PCIN fentanyl is similar in efficacy and safety to oral morphine for relief of procedural wound care pain in burns patients.

Keywords: Intranasal fentanyl; Pain relief; Procedural wound care; Burns

1. Introduction

The impact of a burn injury can be both physically and psychologically devastating [1] compounded by the fact that patients often have to undergo regular procedures such as dressing changes and wound care that can cause severe pain and distress. The ideal analgesic agent for routine wound care in burns patients should provide effective pain relief of rapid onset and short duration, possibly with anxiolytic effects, be easy to administer and have minimal (if any) side-effects [2]. Unfortunately, whilst oral opioids can provide effective analgesic effect, they also have relatively long and unpredictable onset times that can be affected by recent oral intake. They also can have prolonged duration of action (3–6 h) that can substantially exceed the duration of the wound care procedure and result in prolonged sedation [2]. This can negatively impact on return to 'normal' activities by inhibiting ambulation and social interaction. Intravenous opioids can provide effective analgesia, with a shorter half-life of effect, however in order to reduce the risk of infection, it is recommended that intravenous cannulae be removed as soon as possible after the initial resuscitation phase. There has thus been interest in alternative routes of analgesia administration for burns patients.

Striebel et al. [3] found comparable analgesic effects for patient-controlled *intra-nasal* fentanyl (PCINF) and *intravenous* patient-controlled fentanyl (PCIVF) in post-operative orthopaedic patients without patients experiencing problems in using the PCINF device. A recent study

* Corresponding author. Tel.: +61-8-9380-7375; fax: +61-8-9380-1188.
E-mail address: jfinn@cyllene.uwa.edu.au (J. Finn).

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of the pharmacokinetics of intranasal fentanyl found rapid transmucosal absorption, with therapeutic levels achieved within 2 min after a 50 μg in 0.18 ml dose and a bioavailability of around 70% [4].

A pilot study of the feasibility of using patient controlled intra-nasal (PCIN) fentanyl for analgesia during burns dressings was undertaken in the Burns Unit at Royal Perth Hospital in 1996 [5]. Five patients received 5–25 mg of morphine elixir at one dressing change, then 60–120 μg of intra-nasal fentanyl at the next. The patient-controlled intra-nasal analgesia device was filled with 200 μg fentanyl (4 ml) and was administered using a 4 min lockout spray—with each spray containing 9 μg fentanyl. All patients reported equivalence of pain relief for intra-nasal fentanyl and oral morphine. Furthermore, most were welcoming of increased alertness within a short time after completion of the procedure, although one patient complained that he 'missed' the euphoric effects of the morphine [5]. The present study sought to build on this preliminary work to more formally ascertain the efficacy and safety of PCIN fentanyl as an analgesic option for burns patients during procedural wound care.

2. Methods

2.1. Ethics approval

This study was approved by the Royal Perth Hospital Ethics Committee. Informed consent in writing was obtained from all participants.

2.2. Participants

Over an 18-month period beginning in July 2000, adult inpatients (≥18 years of age) of the nine-bed Burns Unit at Royal Perth Hospital, Perth, Western Australia, who required identical wound care procedures (dressing change ± debridement) on two consecutive mornings and were prescribed oral morphine for wound care, were considered for inclusion in the study. The following inclusion criteria applied: English speaking; able to self-administer the intranasal medication; no nasal or inhalation burns; no known allergy to opioid drugs; no intellectual disability or premorbid psychiatric illness; and not receiving intravenous opioid drugs.

2.3. Protocol

Following informed consent, patients were randomly assigned to one of two treatment sequence groups; i.e. A or B, using block randomisation in blocks of four. The randomisation schedule was prepared by the Hospital Pharmacy Department, independent of the investigators. As shown in Table 1, patients assigned to Group A received PCIN fentanyl and an oral placebo during their morning wound care on day 1 and an intranasal placebo and oral morphine on day 2. The sequence for active/placebo treatments was reversed for those in Group B. Individual packs for each patient were clearly labelled with separate drugs for "Dressing 1" and "Dressing 2" by the Pharmacy Department.

Fig. 1. Patient controlled intra-nasal (PCIN) analgesia device.

The Go Medical® [5] patient-controlled intra-nasal analgesia device was used to administer the placebo/fentanyl (see Fig. 1). The device was filled with 4 ml fentanyl (50 μg/ml) and was administered by the patients using a 2 min lockout, with each 0.18 ml spray containing 9 μg fentanyl (when fentanyl was the active agent) and a droplet size of approximately 80 μm. All patients were encouraged to administer four sprays over 8 min prior to the start of the procedure

Table 1
Two-period two-treatment crossover clinical trial

	Group A	Group B
Procedure 1	Active PCIN fentanyl + placebo oral morphine	Placebo PCIN fentanyl + active oral morphine
Procedure 2	Placebo PCIN fentanyl + active oral morphine	Active PCIN fentanyl + placebo oral morphine

(i.e. 36 μg fentanyl when fentanyl was the active agent). Following this 'loading dose' patients were advised to administer further doses as they required, i.e. in a 'patient controlled analgesia' mode. The amount of oral medication administered was as per that particular patients 'usual dose' for wound care, i.e. 25–40 mg (5–8 ml) morphine elixir or placebo, and was administered 30 min prior to the commencement of the dressing.

The placebo formulation for morphine elixir was developed by the hospital Department of Pharmacy to mimic the colour, consistency and bitterness of morphine elixir, thus: Bitrex 0.1% solution 0.1 ml, citric acid 200 mg, sodium citrate 200 mg, glycerol 1 g, compound hydroxybenzoate solution 0.2 ml and purified water to 10 ml. The placebo was tested for similarity to morphine elixir by several consenting patients external to this study. The placebo for fentanyl was normal saline (0.9% NaCl).

Patients self-administered their own fentanyl spray, limiting the risk of opioid overdose. The 2 min lock-out period on the intra-nasal spray device limited the total dose of fentanyl available to the patient to a maximum of 270 μg in 1 h. Pulse rate, respiratory rate and oxygen saturation (SaO_2) was recorded at 10 min intervals throughout the procedure.

Patients continued to receive their 'routine' oral analgesia as per Burns Unit Guidelines, which most commonly was MS Contin 10–30 mg twice daily, ± non-steroidal anti-inflammatory drugs (NSAIDS) and paracetamol. Patients who complained of severe breakthrough pain during the wound care procedure received a 'rescue' dose of morphine elixir as per usual practice. One nurse performed the procedural wound care, often with the patient located initially in the shower, then back in their room. The research nurse recorded pain scores and other observations.

2.4. Outcome measures

2.4.1. Primary outcome

Patient perception of pain intensity was measured using a '0–10' Numeric Rating Scale (NRS), with 0 being "no pain at all" and 10 representing "the worst pain imaginable". NRSs have been shown to be easy to use and similar in sensitivity to the 100 mm Visual Analogue Scale [6]. The patient was asked to select a number from 0 to 10 that best represented the intensity of their pain. Pain scores were recorded at six points in time, namely: (1) prior to the administration of the study medication, (2) prior to commencement of the procedure, (3) during the procedure—around 20 min after commencement, (4) on completion, (5) 10 min after, and (6) 30 min after completion of the procedure.

2.4.2. Secondary outcomes

(a) The patient's overall satisfaction with the level of pain relief achieved throughout the procedure—with '1' representing 'very dissatisfied' and '5' representing 'very satisfied'. (Assessed 10 min after completion of the procedure on each day.)
(b) The Nurse's perception of the patient's level of pain at each of the six points throughout the procedure using the numeric rating scale.
(c) The patient's level of sedation, assessed by the research nurse at several time points, i.e. immediately before the procedure, during the procedure and 10 and 30 min after completion of the procedure, using the hospital's standard tool for assessing drowsiness during patient controlled analgesic use. Sedation was reported as follows: '0' = no sedation—patient wide awake and alert; '1' = mild—occasionally drowsy; '2' = moderate—frequently drowsy, but easy to rouse; '3' = severe, difficult to rouse.
(d) Incidence and severity of any side-effects (e.g. nausea, vomiting, haemodynamic events, or nasal irritation).

2.5. Sample size

The original sample size calculations were based on an overestimate of the correlation of pain scores between the two dressings (0.8 compared with 0.3 actually found) and an underestimate of the standard deviation of pain scores (1.5 compared with 2.5 actually found). Retrospectively the power for this study of 26 patients to detect a mean pain score difference of 2, based on the finding of standard deviations of 2.5 and a correlation of 0.3 for a two-tailed test at 0.05 significance was calculated to be 90%.

2.6. Analysis

It has been customary to recommend that data from crossover studies be examined initially for violation of study design assumptions, such as period and/or sequence effects [7,8]. The recommended approach should a sequence effect be found, has been to confine analysis to the first period only, i.e. essentially converting the study to a parallel study design [7,8]. However, more recently the appropriateness of this practice has been challenged, with suggestion that it can be misleading and biased [9,10].

Thus for this study the two-period crossover design was maintained. A paired *t*-test was used to compare intra-patient pain scores between the PCIN fentanyl and oral morphine procedures. For comparisons of rank order data, such as patient satisfaction, non-parametric tests were used, Mann–Whitney *U*-test for independent groups and the Wilcoxon signed-rank test for paired data. Summary statistics are presented as mean ± S.D., unless otherwise indicated. In all analyses the level of significance was set at 0.05, all tests were two-tailed and 95% confidence intervals (CIs) reported where appropriate. All statistical analyses was conducted on an 'intention-to-treat' basis, however the reporting of adverse events was based on actual drug received. One patient who was randomised to Group B, i.e.

Table 2
Baseline characteristics of patients randomised to Group A (I/N fentanyl first) or Group B (oral morphine first)

Characteristic	Group A: $n = 14$ (fentanyl then morphine)	Group B: $n = 12$ (morphine then fentanyl)	Statistical difference	All subjects
% Male	79%	92%	n.s.	85%
Age (years)	36.4 (±14.6)	34.3 (±9.9)	n.s.	35.5 (±12.4)
Weight (kg)[a]	78.5 (±22.7)	80.3 (±18.7)	n.s.	79.4 (±20.9)
% TBSA	8.0 (±5.3)	5.6 (±3.0)	n.s.	6.9 (±4.5)
Cause of burns	57% flame 36% scald 7% chemical	58% flame 8% scald 25% chemical 8% electrical	$P = 0.027$	58% Flame 23% Scald 15% Chemical 4% Electrical
LOS (days)	9.4 (±4.3)	14.7 (±4.0)	$P = 0.004$	11.8 (±4.9)
Days since admission	3.4 (±1.7)	3.8 (±1.8)	n.s.	3.6 (±1.7)
Duration of procedure (min)	49.3 (±19.5)	43.4 (±37.3)	n.s.	46.6 (±28.6)

Mean ± S.D., unless otherwise indicated.
[a] Missing values for two patients.

oral morphine then PCIN fentanyl, actually received the drugs in the reverse order.

3. Results

3.1. Participants

The characteristics of the 26 patients who completed the study are summarised in Table 2. One additional patient was discharged from hospital prior to the second procedure being performed and was therefore not included in the study. The patients were aged between 18 and 69 years (35.5 ± 12.4 years), with total body surface burns (TBSA) ranging from 1 to 25% (6.9 ± 4.5%), predominantly caused by flame (58%) and scald (23%). The first study procedure was performed between 1 and 7 days after admission to hospital (3.6 ± 1.7 days) and the duration of the wound care procedures ranged from 15 to 150 min (46.6 ± 26.6 min). The length of patient stay in hospital ranged from 2 to 22 days (11.8 ± 4.9 days).

3.2. Medication administered

The number of intranasal sprays that were administered ranged from 2 to 24 with a mean of 12 ± 4 sprays. (Whilst the loading dose was four sprays, one patient felt 'faint' after 2 sprays and hence the procedure for him was abandoned—with no further sprays administered.) The dose of PCIN fentanyl used ranged from 0.34 to 2.47 μg/kg (1.48 ± 0.57 μg/kg). There was no statistically significant difference in the number of sprays used by patients for the active compared with the placebo intranasal agent (mean difference = −0.27 sprays, 95% CI = −1.85 to 1.32, $P = 0.73$). The amount of oral morphine administered varied from 15 to 40 mg (26.0 ± 4.7 mg) with a dose range from 0.17 to 0.78 mg/kg (0.35 ± 0.12 mg/kg).

3.3. Testing of crossover assumptions

There was no statistically significant difference between the mean pain scores during the first dressing procedure compared with the second ($t = -1.19$, 50 d.f., $P = 0.24$), indicating that there was no 'period effect'. However, the overall pain scores for patients assigned to Group A (fentanyl first) were significantly lower than for patients assigned to Group B (morphine first) (3.3 versus 5.2: $t = -2.84$, 50 d.f., $P = 0.007$). Patients who received fentanyl first showed an increase in pain score (albeit not statistically significant) for their subsequent oral morphine procedure whereas the difference in pain scores between the first and second procedure in those patients who received the oral morphine first, was minimal (−1.5 compared with 0.1).

3.4. Pain scores

Fig. 2 illustrates the mean pain scores recorded for PCIN fentanyl procedures compared to oral morphine at various points in time throughout the procedure. Pain scores recorded *during* procedures where PCIN fentanyl was received ranged from 0 to 8, with a mean ± S.D. of 3.78 ± 2.5 and median score of 3.25. When oral morphine was received the pain scores *during* procedures ranged from 0 to 10, with a mean ± S.D. of 4.5 ± 2.6 and median of 5.0. No statistically significant difference was found between the pain scores recorded for patients *during* the procedure with PCIN fentanyl compared to that with oral morphine (paired mean difference = −0.75, 95% CI = −1.97 to 0.47, $P = 0.22$).

No statistically significant difference was found between the intra-subject (PCIN fentanyl versus oral morphine) pain scores (mean difference = −0.14, 95% CI = −0.87 to 0.59, $P = 0.70$) or sedation scores (mean difference = 0.05, 95% CI = −0.24 to 0.33, $P = 0.75$) at 30 min post procedure.

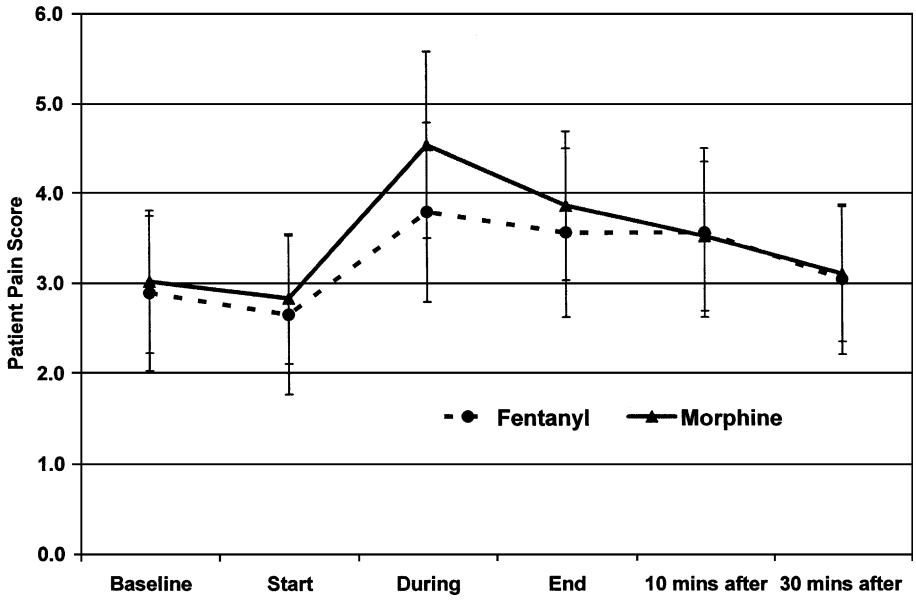

Fig. 2. Comparison of patient's mean pain score (95% CIs) before, during and after procedural wound care for fentanyl and morphine.

3.5. Patient satisfaction

The overall patient satisfaction with the level of pain control achieved during procedures ranged from '1' (very dissatisfied) to '5' (very satisfied), with a mean of 3.5 ± 1.2. Percentiles were as follows: 25th = 2.5, 50th = 3.7; 75th = 4.9. There was no statistically significant intra-patient difference in satisfaction with PCIN fentanyl compared with oral morphine (mean difference $= -0.27 \pm 1.2$, $Z = -0.92$, $P = 0.35$). As per pain scores, no difference in patient satisfaction was found between the first and second procedure (MW = 336.5, $P = 0.978$), however patients randomised to Group A were more satisfied with their level of pain relief than those in Group B (3.9 ± 1.1 versus 3.0 ± 1.2, MW = 195, $P = 0.009$).

3.6. Adverse effects

There was only one adverse event sufficient to justify 'unblinding' of the randomisation code. A 52-year-old male with 5% partial thickness scald burns became giddy, nauseated, and tachycardic (heart rate = 117 from a baseline of 92), with a non-recordable BP on auscultation, 20 min after receiving 25 mg of oral morphine. The patient was reclined in bed and recovered spontaneously after several minutes. There was one other brief episode of hypotension in a 42-year-old male with 2% flame burns who had received 25 mg of oral morphine prior to the second dressing. It was reported that he experienced 'severe pain' whilst the dressing was being removed in the shower, accompanied by a drop in blood pressure from 120/70 to 70/50 and feeling 'faint', which similarly resolved spontaneously.

Two other patients reported feeling nauseated (no vomiting)—one who had received active PCIN fentanyl (first dressing) and one who had received active oral morphine (second dressing).

Only one patient experienced low oxygen saturation. During the first procedure, where oral morphine was the active agent, the SaO_2 dropped to 92%. It is worthy of note however, that the SaO_2 prior to any drugs was only 93%. There was no significant difference in the SaO_2 between fentanyl and morphine groups, before, during or after the procedure.

All but two patients had sedation scores of 1 'mild—occasionally drowsy' or 0 'no sedation'. The other two patients both had a sedation score of 2 at one or more times throughout the procedure, one of these patients had received oral morphine (25 mg) and the other one had received PCIN fentanyl (total dose 70 ìg).

3.7. Rescue analgesia

There were four episodes (in three patients) where 'rescue analgesia' for severe pain was required. A 30-year-old male with 25% burns required an additional 15 mg oral morphine during procedures on both days, having received 117 μg (1.36 μg/kg) PCIN fentanyl on day 1 and 25 mg (0.29 mg/kg) oral morphine on day 2. The duration of the procedures was 45 min and 55 min for days 1 and 2, respectively. The pain scores during the first procedure (PCIN fentanyl) only increased beyond the baseline at 10 and 30 min after the procedure was complete, whereas during the second procedure (oral morphine) the pain scores were unacceptably high (7) during the dressing also.

A 40-year-old male, with 3% full thickness burns required an additional 25 mg morphine during the second dressing, having received a total of 72 mcg fentanyl (1.18 μg/kg). It was noted that the routine morning 'slow release' oral morphine had been given later than the previous day. An

Table 3
Mean pain scores and paired differences in pain scores as assessed by patients and nurses at various points in time throughout the procedure

Time period	Patient	Nurse	Paired difference	95% CI	Significance
Pre-analgesia	2.9	2.3	0.66	0.28–1.05	0.001
Before	2.7	2.1	0.64	0.33–0.96	<0.001
During	4.2	3.8	0.36	0.02–0.70	0.041
End	3.7	3.1	0.65	0.35–0.96	<0.001
10 min after	3.5	2.8	0.77	0.41–1.14	<0.001
30 min after	3.1	2.2	0.88	0.56–1.21	<0.001

18-year-old female patient with 6% partial thickness burns required an additional 15 mg morphine during the second procedure where oral morphine 25 mg (0.37 mg/kg) was the active drug. It was noted that more debridement had been performed than on the previous day, where 146 μg/kg of fentanyl had achieved a better analgesic effect.

3.8. Patient versus nurse pain scores

There was a statistically significant difference in pain scores as assessed by the patient compared with the nurse at all points in time throughout the procedure. As shown by Table 3, nurses tended to underestimate the patients' pain, however this difference was less during the actual procedure than it was before or after. The largest difference (0.9) was seen 30 min after completion of the dressing.

4. Discussion

There was no statistically (or indeed clinically meaningful) difference between intra-subject pain scores for procedures where the active agent was PCIN fentanyl compared with oral morphine. Similarly there was no difference found in the number or nature of adverse events or requirements for 'rescue analgesia'. As concluded in previous studies [3,4,11], intranasal fentanyl would appear to be a safe and effective non-invasive analgesic agent. Whilst half of the patients indicated that they were either 'satisfied' or 'very satisfied' with the level of pain control they experienced, this does mean that half of the patients were less than satisfied, indicating that there is still scope for improvement.

Much of the evidence relating to the efficacy and safety of intranasal fentanyl is based on (non-burn injury) post-operative patients [11–15], the results of which do not necessarily extrapolate directly to burns patients. Three different 'types' of pain associated with burns have been identified, namely: procedural pain, background pain, and breakthrough pain [2,16,17]. Procedural pain, superimposed on pre-existing background pain, specifically in relation to dressing changes and/or wound debridement, is identified as being the most painful experience of all burns treatments and has been described as being severe to excruciating [1,18,19]. Moreover, it has been stated that analgesic requirements are "commonly underestimated" in patients with burns, with standard doses of opioids "likely to be inadequate" in the burned patient [1].

The total amount of fentanyl administered in the present study (1.48 ± 0.57 μg/kg) was comparable to that used in children presenting to an Emergency Department (intranasal fentanyl mean dose = 1.5 μg/kg) [15], but considerably less than that reported for procedural pain in burns (intravenous fentanyl mean dose 8.0 ± 7.0 μg/kg) [20]. The mean TBSA was higher in the Linneman study (mean $17.6\% \pm 18.3\%$) and the age ranged greater, however the authors found no correlation between dosage given and either age or percentage of TBSA [20].

The fentanyl used in this study was as per the commercially available strength of 50 μg/ml and thus only 9 μg of drug was received with each metered spray of 0.18 ml. More recent studies have used a locally manufactured stronger fentanyl solution, with doses of 20 μg/0.18 ml administered to children [15], and 50 μg/0.18 ml in adults [4], administered without any clinically adverse events. It was noted by the research nurse that some patients 'needed reminding' to use their nasal spray—even when they were in pain. It is reasonable to suggest therefore that the use of a stronger fentanyl solution might have yielded even better analgesic effects.

The tendency for nurses to 'underestimate' the severity of the burns patient's pain has been reported elsewhere [21], with suggestion that 'emotional distancing' may be a self-protective strategy adopted by nurses to protect themselves emotionally from the sometimes torturous amounts of pain they inflict on burns patients, in the course of providing procedural wound care [19,22].

No significant differences in sedation levels were found between PCIN fentanyl or oral morphine procedures, however this may be as a result of the relatively crude measurement scale employed, i.e. 0–3. A more valid instrument would be one that incorporates both drowsiness and motivation to participate in activities of daily living/rehabilitation programmes.

Whilst there have been case reports of rhinorrhoea following use of intranasal fentanyl in children undergoing otolaryngologic surgery [23], most clinical studies have not shown this to be a problem [3,4,13]. There was no evidence of nasal irritation reported by patients in our study, however given that the intranasal medication was only administered on two occasions, no longer-term evaluation of this risk can be made.

The two-period two-treatment crossover trial is an efficient study design since it uses patients as their own controls and hence overcomes the problems of inter-patient variability in perception of and response to pain. Whilst there was some suggestion of a sequence treatment interaction, it is not possible to disentangle the effects of the order of testing (sequence) from the timing of the testing (period) [8]. There was no a priori reason to suspect that the order of treatment might affect pain scores, nor any likelihood of a 'carryover' effect from one dressing to the next, given the half-life of the drugs involved. Acknowledging that there is

disagreement as to the best way to proceed when a sequence effect is suspected [7,10], data from the two periods were analysed utilising a 'repeated measures' design.

The exclusion of non-English speaking and non self-harm patients slowed recruitment to the study. Patients were excluded from the study if they had greater than 25% burns, or were receiving intravenous analgesia. Both of these factors may impact on the external generalisability of the study results. Nonetheless, the profile of participants, with an over-representation of adult working age males, with over half caused by flame injuries, reflects the epidemiology of burn injuries in Perth.

5. Conclusions

Patient controlled intra-nasal fentanyl does not differ in safety or efficacy from oral morphine in procedural wound care in burns patients. Pain scores and satisfaction levels would indicate that there is still room for improvement in pain management for patients with burns. It is recommended that PCIN fentanyl, possibly in higher doses than those used in this study, be considered as a viable non-invasive analgesic alternative to oral opioids, for procedural burns pain. Further studies should focus on demonstrating the effectiveness of PCIN fentanyl in this and other patient sub-groups.

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