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Taking the alternative route: Women’s experience of intranasal fentanyl, subcutaneous fentanyl or intramuscular pethidine for labour analgesia.

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Introduction

Many factors influence women’s experience of childbirth, including her response to pain in labour. While most women receive analgesia for labour, the pain experienced by each woman is highly variable (Jones et al., 2012). This unique experience is believed to be affected by not only physiological factors, such as maternal position in labour and mobility, but also psychosocial factors, including levels of fear, anxiety or confidence (Othman et al., 2012). A systematic review undertaken to examine which method of pain relief was most efficacious to women in childbirth concluded suitability of pain relief methods needed to be tailored to each woman’s circumstance, experience and expectation of labour pain (Jones et al., 2012).

In recent years there has been a change in attitude towards labour analgesia. More women are accessing epidural analgesia, whereas, intrapartum opioids such as pethidine are less frequently used (Lindholm & Hildingsson, 2015). Studies that have examined women’s preferences for pain relief during the antenatal period identified women rated pethidine the least preferred pharmacological option due to the potential adverse effects (Henry & Nand, 2004: Madden et al., 2013).
While pethidine is still commonly used for pain management in childbirth, it is reported to produce maternal and neonatal adverse effects. These effects include sedation (Fairlie et al., 1999), vomiting (Ullman et al., 2010), prolonged labour (Khooshideh & Shahriari, 2009), reduced variability of fetal heart rate (Sekhavat & Behdad 2009; Solt et al., 2002), higher incidence of neonatal acidosis (Sosa et al., 2006), reduced Apgar scores (Sharma et al., 2004) and feeding difficulties for up to 6 weeks postpartum (Belsey et al., 1981; Burchell et al., 2016). Furthermore, the Australian and New Zealand College of Anaesthetists has recommended that pethidine use be discouraged in favour of other opioids due to the risk of toxicity from the accumulation of the metabolite norpethidine and associated neuroexcitatory effects that include nervousness, tremors, twitches, multifocal myoclonus and seizures (Schug et al., 2015).

Despite these adverse effects, there are few alternative parenterally administered opioids used for labour pain, with choice limited to what is held at the different hospitals (Lindholm & Hildingsson, 2015). Several recent studies have suggested fentanyl administered by the intranasal (IN) and the subcutaneous (SC) routes is effective for intrapartum analgesia (Fleet et al., 2015; Kerr et al., 2015; Kokki et al., 2015). Advantages of fentanyl include rapid onset of pain relief and no active metabolite to prolong adverse effects (Anderson, 2011). Advances in pain management in other settings have led to the use of these less-invasive techniques of administering fentanyl (Grape et al., 2010; Prommer & Thompson 2011).

While women report increased satisfaction with the use of opioids compared to non-opioids to control labour pain (Othman et al., 2012), practitioners in the obstetric setting continue to debate which opioid and mode of administration provides the most effective pain relief (Ullman et al., 2010). A RCT was undertaken to compare the efficacy of fentanyl administered via different routes, with the standard practice of intramuscular (IM) pethidine use for women in labour. A secondary outcome for this study was to examine women’s breastfeeding experiences and satisfaction with the opiate received. Therefore, this study is the first to describe the experience of women administered fentanyl either intranasally (IN) or subcutaneously (SC) for labour analgesia and to compare these experiences to women who had received IM pethidine.
Participants

Women were eligible to participate if they requested analgesia in labour, had no known medical conditions, an uncomplicated singleton pregnancy in a vertex presentation and were planning a vaginal birth at term (between 37 to 42 weeks gestation). Women were excluded if they had received pethidine or fentanyl within 24 hours prior to the establishment of active labour (regular contractions and a cervical dilatation of at least 3cm) or had a preference for an epidural.

Ethics

Ethics approval was granted by the Children’s Youth Women’s Health Service Human Research Committee on 27 October 2010 and the Southern Adelaide Clinical Human Research Ethics Committee on 14 December 2010 (ethics application number 380.09 and approval number REC2284/9/13). Recruitment occurred from January 2011 to April 2013. Women provided written informed consent in the antenatal period prior to randomisation. Verbal consent was then reconfirmed at time of interview 6 weeks post birth.

Methods

This study represents the third phase of a multi-centred, 3-arm parallel group, non-blinded randomised controlled trial (see detailed methods described in Fleet et al., 2015) that involved a follow up phone questionnaire at 6-weeks postpartum. Women were contacted by telephone by the primary researcher, who had not been involved in the women’s care, to participate in a questionnaire that focused on breastfeeding experience (see Fleet et al 2017), and satisfaction with treatment received. This paper reports the results of the two questions that related to satisfaction with treatment received. Each woman who received treatment, regardless of allocation, was asked whether she would use that form of drug again in a subsequent labour. The question was posed as a dichotomous (yes/no) response. For women who did not elaborate on this question the following prompt was used “Would you like to comment further on your experience of the treatment used?” A summative approach to content analysis was undertaken where comments were transcribed verbatim and coded in a table to identify categories (categorisation) and recurrent words and concepts were grouped (Hsieh & Shannon, 2005).
The occurrence (frequency) of each sub-category was recorded. Categories and sub-categories were confirmed by the co-authors, who also were not involved in data collection while women were in labour.

**Findings**

In total, 112 women provided descriptions of their experience for treatment received. Of whom 41 women received IN fentanyl, 37 women received SC fentanyl, and 38 women received IM pethidine. This includes four women who were randomised to IN fentanyl, but who also received IM pethidine over the course of their labour (due to either a breach in protocol or as rescue analgesia post-treatment).

Maternal characteristics and mode of birth were comparable between groups (see Fleet et al 2017, Tables 1 & 2), with the majority of women being primigravida and experiencing a spontaneous vaginal birth. However, significantly more women in the SC and IN fentanyl groups indicated that they would use the treatment again when compared to women who received pethidine (82.9% IN fentanyl, 80.6% SC fentanyl, 44.8% IM pethidine; p<0.01). When women’s experiences were analysed; three categories emerged—physical, cognitive and emotional effects. These three categories were then classified into sub-categories relating to positive and negative experiences (Table 1). Extracts are included to demonstrate the variations in statements. In addition, examples are provided for statements from women who received both IN fentanyl and IM pethidine.

The majority of statements made by women in the fentanyl groups (87.8% IN fentanyl; 91.9% SC fentanyl) identified at least one of the positive sub-categories for physical, cognitive and emotional effects compared to 50% in the IM pethidine group. Further, 22.0% of women in the IN fentanyl group and 19.0% in the SC fentanyl group reported all three positive categories compared to one woman in the pethidine group. Whereas, the majority of women (89.7%) administered IM pethidine reported at least one negative effect when describing their experience. Even when positive and negative sub-categories were identified, the description of effects differed depending on which treatment and route was administered (Table 1). For example, women who self-administered
intranasal fentanyl reported strong positive emotional responses that demonstrated an increased enjoyment of the experience. While also acknowledging positive physical and cognitive effects.

“Itranasal fentanyl – loved it. I was really happy with it, would recommend it to everyone. I will want to use again and would choose a hospital based on its availability. I found it really helped reduce the pain, felt in control, think it’s brilliant. Didn’t need to use anything else (P.74).”

“I’m really happy with the intranasal, it made contractions feel shorter, still had a peak but better break between contractions but still laboured quickly. Less intense, felt able to cope better (P.51).”

Whereas women who had been administered SC fentanyl were more likely to focus on positive physical effects.

“I really felt the subcutaneous fentanyl helped give me a sense of calm and relaxation between contractions even very close to birthing. Allowed me to focus better and it [subcutaneous fentanyl] helped reduce the intensity of the contraction better than the gas [nitrous oxide and oxygen] (P.138).”

“Subcutaneous fentanyl definitely took away the pain a lot more than the gas [nitrous oxide and oxygen] did, so found it really helpful. Didn’t get any side effects. Found it really helped get me through the labour, I liked the gas at the start, but it wasn’t strong enough. The subcutaneous fentanyl reduced the intensity of the contractions (P.88).”

Responses elicited from women who received IM pethidine were less descriptive and predominately focused on negative physical effects, even when a positive effect such as pain relief was achieved. The following statements demonstrate the variation in description of treatment effects, despite the identification of the same categories.

“The pethidine did give about an hour and a half of pain relief but made me feel really sick (P.30).”
“The pethidine make me very groggy and slowed labour, then it was hard to push but I did need something. Had the gas on strongest, and it wasn’t enough at that stage. So it did give some relief (P.132).”

Route of administration also was a focus of a number of responses. For example, women who self-administered intranasal fentanyl were more likely to report a positive experience and an increased sense of control.

“…. It was great I could self-administer [the intranasal fentanyl], very happy with the effect. Able to time doses well to give maximum benefit. I noticed the difference when I tried not to use it (P.69).”

“Good pain relief and it [intranasal fentanyl] enabled me to walk around and remain alert. It really worked, I was able to get up and walk around. It was great (P.40).”

In comparison, when women were administered SC fentanyl or IM pethidine they needed to wait a specified time due to the longer half-life of the drug and relied on staff to administer the dose.

“The initial [fentanyl 200mcg] dose was very effective. Subsequent [50mcg] dose wore off too quickly. I became anxious waiting for the next dose, would prefer to use intranasal fentanyl next time so could self-administer more frequently (P.2).”

“Really happy with effect from subcut [subcutaneous] fentanyl. Difficult with OP position. Subcut got me through to 9cm…. Smaller doses of [SC] fentanyl didn’t give as much pain relief as first dose which was really effective (P.121).”

“I wouldn’t use [pethidine] again as it only gave a short term effect. It [pethidine] helped a little but I still felt the pain too much. Only worked for a very short time, less than half an hour (P.117).

“I believe pethidine did help a bit with the pain but then it wore off after a short amount of time and as labour was very intense I felt I needed the epidural to give me a break from the pain (P.93).”
Interestingly, when women discussed their experience pain was not always the focus and even on occasions when pain relief was not achieved women still reported beneficial cognitive and emotional experiences.

“I only used the intranasal fentanyl, found it really helpful and would definitely use it again. Intranasal fentanyl really helped me get through. Before it I didn’t think I could continue. Definitely gave a better break and reduced the intensity. Very happy with effect (P.104).”

“Couldn’t feel a change in the intensity of the pain [from IN fentanyl] but did feel I was able to focus better and cope with the contractions. I was much more relaxed when using the intranasal fentanyl despite still experiencing strong pain (P.61).”

“I was more calm with the [subcutaneous] fentanyl. Liked that I could have it (fentanyl) more frequently when needed. Didn’t notice a real difference in pain but did cope better with it (pain) (P.54).”

 “[The SC fentanyl] helped relax me. Would definitely use again, felt it helped me cope. For my previous birth I used an epidural, so happy I was able to do without it (P.110).”

“With pethidine I was more relaxed between contractions, though it [pethidine] was not very effective for pain. I would consider using pethidine again in the same circumstances. Happy with outcome overall, feel it was a good experience (P.63).”

“I’m happy with the effect from pethidine as I don’t feel it [pethidine] had any side effects. Seemed to give a little help (P.123).”

Few women in the fentanyl groups reported a negative effect, but of those who did, negativity was related to not achieving the expected pain relief rather than any adverse effects. For example

“Was difficult to determine real benefit [of intranasal fentanyl] due to rapid birth (P.23).”

“I didn’t feel the intranasal helped (P.28).”

“Really difficult to tell if it [SC fentanyl] helped as baby born within 20 mins of dose (P.43).”
“Don’t feel it [SC fentanyl] really helped with the pain, happy though there were no side effects. Had used pethidine in a previous birth and wouldn’t want to use pethidine again because of the side effects (P.136).”

In comparison, negative experiences were commonly reported by women in the IM pethidine group and were commonly related to negative physical effects.

“The pethidine knocked me out. It [IM pethidine] didn’t help with the pain. Made me sleep between contractions but wasn’t a good experience (P.8).”

“Felt really out of it even after the birth. Don’t recall that it gave a reduction in pain. Felt distant and dissociated with birth. Don’t even remember the early period after birth, looked at photos and didn’t remember it happening. Disappointed with effect (P.137).”

Of the four women who received both IN fentanyl and IM pethidine, all four women commented that IN fentanyl provided more pain relief than IM pethidine. For example, Participant 7 requested alternative analgesia after 2 hours of IN fentanyl use and was administered IM pethidine. Both negative physical and cognitive experiences were reported with the use of IM pethidine, whereas positive emotional experience was identified from the description of the IN fentanyl use.

“Pethidine slowed everything down. I really didn’t like the experience – I felt really out of it. At the time I wasn’t sure if the intranasal fentanyl was still helping but after using the pethidine I was more aware that it had been, without causing the high or sedation (P.7).”

Participant 44 had been administered pethidine overnight when labour established and then randomised 7.4 hours later to receive IN fentanyl, an hour before she gave birth. Both positive emotional and cognitive descriptions were reported with the use of IN fentanyl. This contrasts to the negative cognitive and physical experience reported about the use of IM pethidine.

“I really liked the intranasal (fentanyl) spray I felt able to cope and focus, it allowed me to push as I had been overwhelmed with the whole induction and frequency of contractions and couldn’t do anything due to constant pain, there was no break between contractions. Pethidine though made me feel out of it. I kept falling asleep and not remembering what I was
doing. The gas was also horrible it made me feel out of control. I couldn’t have done it without the intranasal fentanyl (P.44).”

Discussion

When the comments were grouped into categories and sub-categories, the positive sub-categories were seen most often in women from the fentanyl groups. The positive emotional sub-category was identified with greater frequency among women in the IN fentanyl group, compared to women in either the SC fentanyl or IM pethidine groups. Both fentanyl groups had only low frequencies of negative sub-categories. In contrast, women in the IM pethidine group had greater frequency of all three negative sub-categories, with negative physical effects being identified most often (Table 1).

Women in the IM pethidine group most often reported negative physical effects from treatment and equivocal positive and negative emotional experiences. Only one other study was identified that specifically explored women’s experiences of opioid analgesia use during labour (Jantjes et al., 2007), and identified findings similar to this study. Jantjes et al. (2007) examined the emotional experiences of primipara women who used pethidine combined with an antihistamine, hydroxyzine, during labour. Their findings suggest that women’s experiences from using pethidine varied significantly from expressions of joy and happiness to anxiety, anger and despondence (Jantjes et al., 2007), further highlighting the potential for pethidine use to provoke contrasting emotional responses.

Satisfaction with the drug, and hence intention to use the treatment again, may also have been influenced by the reduced prevalence of adverse effects and the ability to mobilise (Ross, 1998). In this study, participants in the fentanyl groups reported fewer adverse effects than those in the pethidine group. In addition, women in the fentanyl groups reported the ability to mobilise, possibly due to less sedation. This mobility may have allowed them to adopt a variety of positions to help ease painful contractions. In contrast, women who received IM pethidine reported adverse effects such as nausea, sedation and feeling dissociated which may have reduced their ability to ambulate.

The technique and timing of administration is another aspect that requires further investigation and may have contributed to the woman’s overall experience. While it was not considered ethical to blind
this study as it would entail participants receiving all three routes of administration, preference for the route received may have affected the woman’s perception of autonomy (McNicol et al., 2015). This may in part also explain the positive comments made by women in relation to IN fentanyl, which was administered using a patient controlled intranasal applicator device. Patient controlled analgesia has been shown to produce greater satisfaction and analgesic effect in women (Schug et al 2015). In addition, route of administration may be affected by a placebo effect (Hui et al., 2014). For example, a placebo effect could be influenced by the participants’ expectations that a treatment would provide benefit and/or by the practitioners’ expressed attitudes towards the treatment provided (Porto, 2011). Further research should consider participants’ expectations prior to treatment, as well as how practitioners’ involvement in care may influence these expectations. This is particularly important as models of care, such as continuity of carer has been associated to improve maternal satisfaction, reduce anxiety and the need for pharmacological forms of pain relief (Leap et al 2012).

**Conclusion**

In this study self-administration of intranasal fentanyl in labour resulted in positive emotional experiences with women often commenting on their sense of control and autonomy. Whereas, women who were administered SC fentanyl were more likely to describe the positive physical effects of the treatment. Fentanyl administered by the IN or SC routes offers women additional choices for pain relief in labour that are less invasive than traditional methods. Route of administration should be discussed when choice of analgesic agent is offered and may further contribute to a positive birth experience.

**Ethical Statement**

**Conflict of Interest**
The authors Julie-Anne Fleet, Ingrid Belan and Meril J Jones have no conflict of interests to declare.

**Ethical Approval**

Ethics for this study was granted by the Children’s Youth Women’s Health Service Human Research Committee on 27 October 2010 and the Southern Adelaide Clinical Human Research Ethics Committee on 14 December 2010 (ethics application number 380.09 and approval number REC2284/9/13).

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**References**


Table 1  Women’s experience of treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Sub-categories</th>
<th>Frequency of distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IN fentanyl</td>
</tr>
<tr>
<td>Physical experience</td>
<td><strong>Positive</strong>: Excellent pain relief/ relieved pain/ more pain relief than gas/ enabled relaxation/ better break/ able to be mobile</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td><strong>Negative</strong>: Gave no relief/ didn’t help at all / wore off too quickly/ slowed everything down/ not strong enough/ felt sedated/ sick</td>
<td>8.2</td>
</tr>
<tr>
<td>Cognitive experience</td>
<td><strong>Positive</strong>: Felt alert/ better focused/ felt really connected/ gave a sense of calm / better able to cope/communicate/ felt more in control</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td><strong>Negative</strong>: felt out of it/ didn’t have a good experience/ not remembering/ distant/ disassociated</td>
<td>0</td>
</tr>
<tr>
<td>Emotional experience</td>
<td><strong>Positive</strong>: loved it/ perfect/ promoted it / amazing/ great/ really helped/ happy/ wonderful/ impressed/ enabled me/ didn’t need an epidural/ better than an epidural</td>
<td>45.2</td>
</tr>
<tr>
<td></td>
<td><strong>Negative</strong>: lost confidence/ left feeling fearful / anxious/ disappointed/ didn’t help/ didn’t like it / preference for gas or epidural</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Percentage (%) reflect number of comments made by participants.
Highlights

- This study is the first study to describe the experience of women administered intranasal and subcutaneous fentanyl for labour analgesia.
- Women who self-administered intranasal fentanyl reported positive emotional responses that demonstrated increased sense of autonomy and satisfaction, compared to women administered either subcutaneous fentanyl or intramuscular pethidine.
- Responses from women who received pethidine predominately focused on negative effects, even when pain relief was achieved.