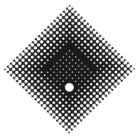
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Patient-controlled intranasal fentanyl analgesia: A pilot study to assess practicality and tolerability during childbirth

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Highlights

- Intranasal self-administration of fentanyl was associated with few maternal side effects.
- A trend for increased adverse events and neonatal respiratory support occurred with higher doses.
- The majority of women reported a willingness to use this analgesic option in the future.

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Title

PATIENT-CONTROLLED INTRANASAL FENTANYL ANALGESIA: A PILOT STUDY TO ASSESS PRACTICALITY AND TOLERABILITY DURING CHILDBIRTH.

Short Title

Patient-controlled intranasal fentanyl analgesia for childbirth

Author names and affiliations

D. Kerr[a], D. Taylor[b], B. Evans[b]

a. College of Health and Biomedicine, Victoria University, St Albans, Victoria, Australia, 3021

b. Western Health, Private Bag, Footscray, Victoria, Australia, 3011

Corresponding author

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Corresponding Author

Name: Associate Professor Debra Kerr

Department: College of Health and Biomedicine

Institution: Victoria University

Mailing address: Victoria University, 4th Floor, McKechnie St, St Albans, Victoria, Australia, 3021

Phone: +61 3 9919 2053

Fax: N/A

Email: deb.kerr@vu.edu.au

ABSTRACT (n= 250)

Background:

Intranasal administration of fentanyl is a non-invasive method of analgesic delivery which has been shown to be effective for relieving pain. This pilot study aimed to assess the practicality and tolerability of patient-controlled intranasal fentanyl for relieving pain during childbirth.

Methods:

This prospective, non-randomised, clinical trial recruited women with a singleton pregnancy during November 2009 to October 2011. Exclusion criteria included respiratory disease, gestation <37 weeks and pregnancy complication. The device administered 54 mcg of fentanyl per spray, incorporating a 3-minute lock-out. Data included demographics, dose, additional analgesia, adverse events, pain relief and delivery outcomes. Follow-up data was obtained within 48 hours regarding tolerability of the device. Data is presented as descriptive statistics.

Results:

The final sample included 32 women: mean age 28.7 years and gestation 39.8 weeks. Average fentanyl dose was 733.9 mcg and duration of use was 3.5 hours. Most women (78.2%) reported 'satisfactory' to 'excellent' pain relief using the nasal device. Four neonates (12.5%) required bag-mask ventilation at birth: three had adequate respirations within 5 minutes and 1 required short-term observation in special-care-nursery. For all items, there was a trend towards an adverse outcome, including neonatal respiratory support, as the dose increased. On follow-up, 84.4% reported they would use intranasal fentanyl for their next childbirth experience.

Conclusions:

Patient-controlled intranasal fentanyl provides an acceptable level of analgesia during childbirth, however, may increase the risk of respiratory depression for neonates. Future, randomised studies might evaluate the safety and efficacy of patient-controlled intranasal fentanyl compared with existing analgesia options.

Key-words: analgesia, childbirth, fentanyl, intranasal, obstetric, patient-controlled.

INTRODUCTION

Birthing may be the most severe pain experience for most women. In Australia, various methods of analgesia are available to birthing women, including pharmacological (systemic and epidural analgesic)[1-3] and non-pharmacologic techniques (e.g. continuous birthing support, aromatherapy, intradermal water injections, hydrotherapy, massage, acupuncture, maternal movement and positioning).[2,4]

Systemic birthing analgesia includes inhaled nitrous oxide and systemic opioids. In Australia, pethidine has been the traditional opioid of choice.[5] Opioid administration is associated with maternal side effects including nausea and vomiting, respiratory depression, and delayed gastric emptying. All opioids cross the placenta, and can result in neonatal side effects including respiratory depression, inhibition of suckling, lower neurobehavioral scores, and delay in effective feeding.[6]

Doubt has been cast on the suitability of opioid analgesia for birthing pain because of the high incidence of maternal and neonatal adverse effects and inadequate analgesia it provides.[2] In addition, there are considerable doubts about the effectiveness of pethidine including the slow onset of action.[7] A recent Cochrane review identified a lack of research regarding the efficacy of opioid analgesia, which opioid is most effective, and strategies to minimize adverse side effects.[8] At best, they found moderate maternal satisfaction with opioid analgesia.

Currently the options for effective labour analgesia are limited. Prolonged and unrelieved pain may cause patient dissatisfaction and is associated with postpartum depression and posttraumatic stress disorder.[9,10] The 'gold standard' for birthing analgesia is epidural analgesia, which provides superior analgesia without maternal sedation.[2] However, many women choose not to have an epidural and some women are unable to have an epidural due to co-existing contra-indications (e.g. coagulopathy, spinal pathology), fear of needles, and absence of skilled staff (e.g., an anaesthetist to insert the catheter or midwifery staff trained in the management of epidurals, etc). Epidural analgesia is associated with an increased risk of instrumental vaginal delivery, prolongation of second stage and increased oxytocin requirement.[11] Leeman et al.[12] questioned if the high use of epidural analgesia is really the true preference among women in the United States or if it is chosen because there is a lack of acceptable options. They recommended further research investigating women's preferences regarding analgesia during childbirth.

Fentanyl is a synthetic opioid analgesic and may be administered via several routes, most commonly via epidural injection or intravenously (IV), both of which are invasive. After neuraxial block, women may be restricted to bed and have limited mobility for a significant period of time which may impact negatively on maternal satisfaction and delivery.

Drugs, including fentanyl, may cross the placenta to the fetus. However, serum fentanyl levels in the fetus have been found to be significantly lower than maternal serum levels. Furthermore, respiratory depression has been found to be rare in babies born to mothers receiving fentanyl either parenterally or via an epidural.[13-15]

Maternal satisfaction during birthing has been widely studied. Behaviours that encourage involvement and participation in decision-making during birthing promote feelings of control, coping and feeling supported, facilitating a woman's assessment of their birth experience as positive.[16] Patient-controlled epidural analgesia has been associated with improved maternal satisfaction and lower volume of local anaesthetic requirement compared with continuous epidural infusion.[17]

Intranasal fentanyl has been proposed as an alternative, fast-acting and non-invasive method of analgesia and has been shown to be effective in relieving pain for various conditions including acute and chronic pain[18-21], burns pain[22, 23], post operative pain[24-26], and breakthrough cancer pain.[27] Fentanyl administration via intranasal patient controlled analgesia (PCA) has been found to be as effective as IV PCA for post operative analgesia.[26, 28] To our knowledge, self-administered intranasal fentanyl has not been used in the obstetric setting.

The administration of patient-controlled intranasal fentanyl (PCINF) may positively affect the birthing experience by virtue of being less invasive and portable, having a short duration of action and effectively relieving childbirth pain. This pilot study aimed to assess the practicality and tolerability of PCINF for relieving birthing pain.

METHODS

Design

This was a prospective, non-randomised, open clinical study registered with the Australian and New Zealand Clinical Trials Registry. Ethics approval was obtained from the Melbourne Health Human Research Ethics Committee. Informed and written consent was obtained from all participants in the ante-natal period.

Recruitment

Women were recruited from one hospital site during November 2009 to October 2011. With over 3500 deliveries per year, it was at the time of the study the third largest obstetric facility in the major metropolitan area. Women who presented to this facility for antenatal care and who fulfilled the study criteria were provided with information about the clinical trial from a midwife during their clinic assessment.

To be eligible, women had to be at least 18 years of age and 37 weeks gestation at the time of presentation and in labour. In addition, they needed to be able to self-administer PCINF and speak and read English. Exclusion criteria included: 1) presence of pregnancy–related medical condition (e.g. pregnancy induced hypertension, pre-eclampsia, gestational diabetes); 2) abnormal fetal lie (e.g. breech); 3) placental abnormalities detected during ante-natal assessment; 4) non-singleton pregnancy; 5) allergy to opioids; 6) asthma; 7) myasthenia gravis; 8) opioid tolerance (e.g. regular use of methadone, buprenorphine, heroin, morphine, oxycodone) and 9) chronic nasal problems (e.g. hay-fever, sinusitis). Eligibility criteria were re-assessed by the treating midwife. Women who had previously consented to participate, but when they presented in labour had an exclusion criteria (for example; pre-eclampsia or breech presentation, etc), were no longer eligible.

Intervention

Women fulfilling all study criteria were able to request a PCINF device for pain relief after presenting to the delivery suite in labour. The devices were prepared in advance and available for all women at hospital presentation. Women were informed that they had no obligation to use the PCINF device and that it was available as an analgesic option if, and when, they requested it.

Fentanyl (300mcg per mL), manufactured and supplied by Orion Laboratories (Western Australia, Australia), was used to fill the Go Medical nasal pump device, purchased from Admedus, Australia (Figure 1). The single use PCINF devices, as prepared for this study, contained 450mcg of Fentanyl (1.5ml) in total, delivered 54mcg (0.18mL) per atomised spray thus enabling eight atomised sprays per device. Following demand activation, the device flow control tubing is re-loaded over 3 minutes. During this refill interval, a partial pro-rata dose can be delivered by pump activation, thus limiting the frequency of full dose administration. At the time of the study, St John Ambulance guidelines (Western Australia) recommended a loading dose of 180mcg, followed by 56mcg boluses at 5-minutely intervals. (Informal evidence, 2010) We proposed 54mcg at 3-minute intervals with no loading dose, in lieu of severity of pain and requirement for more frequent doses, in comparison to patients receiving care in an ambulance for a short period of time.

Several safety precautions were exercised including frequent vital sign assessment, restricted volume in a single device and a limit of four devices per participant. To monitor for opioid-induced ventilatory impairment (OIVI), participants were monitored continuously by their allocated midwife for sedation, respiratory rate, heart rate, blood pressure, pulse oximetry and fetal heart rate. OIVI, assessed by respiratory rate and sedation score, was determined between contractions. Sedation score was assessed according to standard hospital assessment procedures and the following criteria: “Alert”, “Mild” (sometimes drowsy, easily roused, stays awake once woken), “Moderate” (often drowsy, easily roused, unable to stay awake once woken), “Severe” (Often drowsy, difficult to rouse or a

respiratory rate <10), or "Asleep" (stirs to touch). Use of the PCINF device was discontinued for any woman who experienced moderate or severe sedation, along with increased frequency of observations and oxygen administration.

Due to pain severity[5], we estimated that women in this study would require higher doses of fentanyl than may have been used to manage other types of pain. After completing one device a woman was provided with a further PCINF device provided she did not show significant adverse effects including opioid-induced ventilatory impairment (moderate or severe sedation and/or respiratory rate < 10/min), systolic blood pressure < 90mmHg, heart rate < 50 beats per minute, nausea and/or vomiting not relieved by anti-emetic or abnormal fetal heart rate or variability. Initially, a limit of four PCINF devices was set (maximum possible fentanyl dose of 1800mcg). This maximum allowable dose was revised down to 1350mcg following the observation that three women experienced a moderate level of sedation at the higher dose. Standard practice in the birthing unit in which this study was conducted was that Pethidine is given relatively early in labour, and then avoided as labour progresses, so as to reduce the risk of neonatal opioid side effects. Midwives carefully assess women's progress in labour and the appropriateness of administering opioid analgesia. When women are judged to be in transition, opioid analgesia is usually withheld. In keeping with standard practice, PCINF administration was suspended during second stage of labour.

The woman and her support person(s) were educated about use of the PCINF device, including instructions not to share the device and its' contents with another person. The PCINF was carried by the participant in a pouch supported by a lanyard fastened around their neck for easy access during mobilisation. Women were advised that the device would not totally alleviate their pain and that they should discontinue self-administration if they felt excessively drowsy or light-headed. In addition, vital signs were measured at 30-minute intervals to detect hypotension.

Trial participation did not preclude women from requesting and receiving other modes of pain relief including intramuscular pethidine, nitrous oxide and epidural analgesia. However, PCINF was discontinued before alternative opioid analgesia or epidural analgesia was administered. Women were able to co-administer nitrous oxide and PCINF.

Data Collection

An explicit data form was used by midwives during PCINF use to record information related to the study. Data were collected by midwives and included: demographic data (age, ethnicity, primary language spoken), pregnancy-related information (birthing support, induced or natural labour, parity, gestation) and routine observations. Throughout use of the PCINF device routine observations were recorded at 30-minutely intervals including vital signs (heart rate; blood pressure; oxygen saturation;

respiratory rate), sedation score, fetal heart rate and any adverse effects. The number of PCINF devices used, additional analgesia administered, difficulties with use of the device and mode of delivery were documented. After delivery, neonatal outcomes including Apgar score at birth and at 5-minutes, and the requirement for respiratory support or naloxone were also recorded.

The primary outcome measure was pain relief using a subjective measure. Pain relief was measured between contractions at 30-minute intervals using a 5 point Likert-type scale (a lot, moderately, a little bit, not at all, not sure). These descriptions for pain relief were used in this study to simplify explanations of the pain scale to women during labour. Within 24 to 48 hours of delivery, women were interviewed in hospital or by telephone to obtain the following data: adverse effects; ease of use; and intention to use PCINF for future births. Women were also asked whether they would use PCINF in future birthing episodes.

Data analysis

IBM SPSS for Statistics[29] was used for data storage and analysis. Mean and range are presented for continuous data which was normally distributed and proportions for categorical data. This was a pilot study designed to test the practicality and tolerability of PCINF for women during childbirth; therefore no sample size estimation was calculated prior to conduct of the study, nor were differences compared by univariate analysis.

RESULTS

Seventy-nine women were recruited to participate in the study in the antenatal period. However, 44 women did not use the PCINF device for reasons including analgesia not required, elective caesarean section, or alternative analgesia use. In addition, three further women were excluded from participation for reasons including emergency caesarean, presentation in second stage and faulty device. In regards to the faulty device, contents of the vial were not expelled after depression of the vial. The woman declined to accept a new device and opted for alternative analgesia.

The final sample included 32 women with a mean age of 28.7 years and gestation of 40 weeks. Fentanyl use, demographics and birthing characteristics are shown in Table 1. The average fentanyl dose was 733.9 mcg and duration of use was 3.5 hours. Nineteen (59.4%) used nitrous oxide in addition to PCINF. Nine women (28.1%) discontinued PCINF use when they requested alternative analgesia (pethidine (2, 6.3%) and epidural (7, 21.9%).

Maternal and neonatal outcomes are provided in Table 2. Pain relief was achieved, as an average for duration of PCINF use, in the following proportions: “A lot” (26.2%), “Moderately” (21.6%), “Little Bit” (27.9%), “Not at all” (18.7%) and “Not Sure” (2.1%). On follow-up, 27 women (84.4%) reported

they would ask for PCINF device for future birthing experiences. When asked about the overall impact on pain relief during birthing, the majority of participants (78.2%) found PCINF to be at least satisfactory for relieving pain (excellent: 34.4%, good: 21.9%, satisfactory: 21.9%). Twenty-eight women (87.5%) found the device easy to use.

Three women (9.4%) were moderately sedated after using PCINF, resulting in discontinuation of PCINF treatment. For two of these women, the neonate had a low Apgar score at birth (3 and 4) but achieved an adequate score within 5 minutes after birth (8 and 9). Thirteen (40.6%) women experienced adverse effects, including nausea (31.3%), vomiting (31.3%), headache (3.1%) and nasal irritation (12.5%).

The majority of infants had an Apgar score of at least 7 at birth (84.4%) and at 5 minutes (93.7%). Ten neonates (31.3%) required some form of respiratory support at birth. Additional detail regarding these neonates is provided in Table 3. Positive pressure ventilation (Neo-Puff) was administered to four neonates with Apgar scores of 1, 3, 4 & 7 at birth. These scores improved within 5 minutes (6, 9, 8 & 9; respectively). One neonate with concurrent heart murmur and congenital ear problems was transferred to special care nursery for ongoing assessment. Continuous positive airway pressure (CPAP) using air was administered to six neonates, who all recovered without requirement for naloxone. Without diminishing the fact that approximately a third of neonates (n=10) in this study experienced an adverse outcome, eight (Table 3) had a co-existing factor which might have contributed to their adverse condition. In the neonates who required respiratory support at birth, the following factors were co-existent: cardiotocography (CTG), deceleration (n=2), meconium staining (n=2), cephalo-pelvic disproportion (CPD) (n=2), cord around neck (n=1) and shoulder dystocia (n=1).

Adverse outcomes including low Apgar scores (<7) at birth, requirement for neonate respiratory support (CPAP or NeoPuff), and moderate maternal sedation in relation to cumulative fentanyl dose, are presented in Table 4. For all outcomes, there was a trend towards an adverse outcome as the dose increased.

DISCUSSION

To our knowledge, this is the first study to assess PCINF use during birthing. This pilot study found that PCINF using a 3-minute lock-out device provided a high level of satisfaction for women during childbirth. The majority of participants (84.4%) expressed a willingness to use PCINF in future birthing experiences. One of the distinct advantages of PCINF lies with its' application as a self-administered analgesic. McCrea and Wright[30] found that feelings of personal control positively influence women's satisfaction with pain relief during birthing. A study by Fenwick et al.[31] confirmed

that women prefer to be involved and to participate in decision making during their birthing experience. So it may be that the main advantage of PCINF lies with its' application as a self-administered analgesic, facilitating a sense of self-efficacy. This would require further investigation.

While the device was acceptable to most of the participants, it is interesting that approximately half of them rated it as providing little to no relief of pain when evaluated between contractions. A recent Cochrane review[32] found that there is insufficient evidence regarding the effectiveness of parenteral opioids, and high quality trials are needed. Pharmacologic options for women in Australia are limited to inhaled nitrous oxide , intramuscular opioid, IV PCA opioid and epidural analgesia. Nitrous oxide inhalation provides minimal pain relief.[2] Intramuscular injections are painful and opioids may be associated with unpleasant side effects for both mother and baby including nausea, vomiting, sedation and respiratory depression.[2] Fleet et al[33] have recently reported that intranasal fentanyl was associated with less sedation scores, anti-emetic use, and epidural use, and higher requirement for nursery admission for neonates, compared with women receiving pethidine during labour. In that study, intranasal fentanyl was also associated with greater satisfaction. Epidural infusion may be difficult or contra-indicated, may restrict the woman to bed rest or delay birthing.[2] It is possible that the PCINF device does not offer further benefit when compared with IV PCA fentanyl, aside from not requiring a cannula and the related risk of infection. Pharmacokinetic studies comparing intranasal and IV administration have shown that onset and duration of analgesia are similar[34-35]. Some of the benefits of IV PCA over a nasal device include better titratability of administered dose and total hourly dosage. The portability and accessibility of a nasal spray however makes this mode of delivery more accessible to women in remote areas. One PCINF device costs approximately $47 Australian dollars, which makes this an affordable analgesic option. Future studies may compare these two modes of administration.

A high rate of nausea and vomiting was found in this current study (nausea, 31.3%, vomiting, 28.1%). More than half (59.4%) of the women used nitrous oxide inhalation which may also be associated with these side effects and contributed to analgesia also. In an informal audit, Sinha et al.[3] found that 50% of women in birthing felt nauseated or vomited. Hence, it is unclear if side effects experienced were in response to fentanyl alone, nitrous oxide alone or both, or was a normal physiological response to the visceral pain of birthing. It is likely to be multifactorial.

In this study, ten babies (31.3%) required respiratory support after birth. In response, the study protocol was amended to a limit of 1350mcg for the duration of 1st stage, cessation of PCINF use in 2nd stage, and discontinuation if the woman had moderate or severe sedation, or had a respiratory rate less than ten. No neonate received naloxone throughout the study period & none required Neopuff support after the protocol amendment. There was a suggestion that higher doses of fentanyl were

associated with an increased requirement for neonatal respiratory support and maternal sedation. Statistical testing of this trend was not performed due to low numbers. Whilst most newborns are vigorous at birth, the Australian Resuscitation Council reports approximately 10% will require some breathing assistance at birth[36]. Halpern et al.[37] found that 52% of neonates required active resuscitation and 17% required naloxone treatment after IV Fentanyl PCA. This would suggest that PCINF is not inferior to IV PCA Fentanyl. For neonates who required respiratory support at birth, 8 (80%) had confounding variables which may also have contributed to the requirement for resuscitation e.g., meconium staining, CPD, cord around neck or dystocia.

Our study found that women in childbirth used higher doses of Fentanyl (mean: 733.9mcg) when compared with the pre-hospital (mean dose: 362mcg) setting.[38] In a small study evaluating the use of patient controlled intranasal fentanyl over 8 hours post caesarean, the maximum dose administered was 319.5 mcg.[39] Reasons for the higher dose used in our study may be the prolonged duration of PCINF use (duration of use: mean 3.5 hours, range 1 to 14 hours) and known severity of intra-partum pain. Higher doses have been reported in studies investigating IV Fentanyl PCA[33, 40] The findings of this study may also have been affected by the fact that over one-third of participants had labour augmented with oxytocin, which may have had a significant impact on pain scores and satisfaction with the device. Larger, randomised studies should be able to control for confounding factors such as concomitant analgesia use (e.g., nitrous oxide) and other treatment (e.g., oxytocin).

LIMITATIONS

A moderate proportion of women who consented to participate in the ante-natal period, did not use the PCINF device during childbirth, possibly because they changed their mind about participating in the study or because they did not require analgesia during childbirth. Extensive exclusion criteria limited enrolment to mainly healthy women. Difficulties in recruiting participants during the antenatal period has been reported previously.[41] A follow study could investigate women's opinions about the use of PCINF during birthing. In addition, this was a small pilot study involving 32 women over a 2-year period, and over half (59.4%) of the women used nitrous oxide inhalation which confounds the data.

Conclusion

Intranasal self administration of fentanyl in birthing was acceptable to the majority of participants with few significant maternal side effects, most of which are known to be associated with systemic opioid analgesics as a class. However, there was a trend for increased adverse events and requirement for neonatal respiratory support with higher doses.

There are limited pharmacologic choices for women during childbirth. Self-administered nasal fentanyl does not compel a woman to bed rest, and may provide a degree of autonomy during the

birthing experience. A large, randomised study comparing PCINF with other analgesic preparations (e.g. opioid injection, inhaled nitrous oxide) is required to more fully explore the efficacy and safety of PCINF.

Table 1 Demographic and Birthing Characteristics and Fentanyl Use

Characteristics			
		Mean	**Range**
Age (years)		28.7	18 to 39
Gestation (weeks)		39.8	39 to 41
		21	65.6%
		3	9.4%
		2	6.3%
		2	6.3%
		4	12.6%
		Mean	Range
Average Fentanyl dose (mcg)		733.9	90 to 1800
Duration of PCINF[1] use (hours)		3.5	1 to 14
Duration of labour (hours)	1st Stage	11.6	2 to 26
	2nd Stage	0.8	0.3 to 3.5
		No:	**%**
Previous births		28	89.9%
Country of birth	Australia/New Zealand	21	65.6%
	Asia	3	9.4%
	India	2	6.3%
	Europe	2	6.3%
	Other	4	12.6%
Augmentation	Nil	16	50.0%
	Prostaglandin	5	15.6%
	Rupture of membranes	1	3.1%
	Oxytocin	12	37.5%
Nitrous Oxide		19	59.4%
Mode of Delivery	Normal Vaginal delivery	19	59.4%
	LUSC[2]	8	25.0%
	Instrumental	5	15.6%

1. PCINF: Patient controlled intranasal fentanyl, 2. LUCS: Lower uterine segment caesarean

Table 2 Ante-natal and post-natal outcomes during patient controlled intranasal fentanyl use

Maternal Outcomes		**Proportion**	**Range**
Average proportion of pain relief during PCINF[1] use for the sample	A lot	26.2%	0 to 100
	Moderately	21.6%	0 to 100
	Little Bit	27.9%	0 to 100
	Not at all	18.7%	0 to 33.3
	Not sure	2.1%	0 to 2.1
		No:	**%**
Analgesic Efficacy	Excellent	11	34.4%
	Good	7	21.9%
	Satisfactory	7	21.9%
	Poor	3	9.4%
	Very Poor	2	6.3%
	Not sure	2	6.3%
Side effects			
	Moderate sedation	3	9.4%
	Nausea	10	31.3%
	Vomiting	10	31.3%
	Nausea or vomiting	13	40.6%
	Headache	1	3.1%
	Nasal irritation	4	12.5%
Reason for withdrawal			
	Pethidine or Epidural	8	25.1%
	LUSC[2]	6	18.8%
	Sedated	2	6.3%
	Second Stage	5	15.6%
Neonatal Outcomes		**No:**	**%**
Apgar Scores at 1-minute	1 to 3	3	9.4%
	4 to 6	2	6.3%
	7 to 10	27	84.4%
Apgar Scores at 5-minutes	1 to 3	0	
	4 to 6	2	6.3%
	7 to 10	30	93.7%
Requirement for CPAP[3]	10	31.3%	
		Mean	**Range**
Time to established respirations (minutes)		1.6	1 to 8

1. PCINF: patient-controlled intranasal fentanyl; **2. LUSC: Lower uterine segment caesarean section; 3. CPAP: Continuous Positive Airways Pressure**

Table 3 Summary of respiratory support for ten neonates

Respiratory Support	APGAR		Fentanyl Dose micrograms	Fentanyl duration (hrs)	Labour Duration		Birth weight	Delivery	Birthing or Neonate Complication
	Birth	5 mins			1st Stage (hrs)	2nd Stage (mins)			
Neo-Puff	1	6	1350	7	7.8	30	4740g	Instrum[1]	Deceleration, Shoulder dystocia
Neo-Puff	3	9	150	1	9.8	20	3430g	NVD[2]	Deceleration, Precipitate delivery
Neo-Puff	4	8	1690	7	8.5	17	3720g	Instrum	Deceleration, Heart murmur, Ear canal malformation
Neo-Puff	7	9	450	4	16.0	80	3205g	Instrum LUSC	Deceleration, Meconium
CPAP[3]	3	8	900	4	9.0	16	3820g	Normal	Nil
CPAP	7	9	1350	7	21.0	NA	3610g	LUSC	CPD[4], Deceleration
CPAP	7	9	660	4	14.0	195	3780g	Instrum	Deceleration, Meconium
CPAP	8	9	900	3	20.0	189	4710g	LUSC	CPD, Meconium
CPAP	8	8	600	3	7.0	36	3650g	NVD	Nil
CPAP	9	6	750	2	2.0	40	3950g	NVD	Shoulder dystocia, Cord around neck

1. Instrum: Instrumental; 2. NVD: Normal vaginal delivery; 3. CPAP: Continuous positive airway pressure; 4. CPD: Cephalo-Pelvic Disproportion

Table 4 Comparison of Apgar scores at birth, requirement for respiratory support, maternal sedation and duration of use by fentanyl dose.

Fentanyl dose (microgram)	Total No n (%)	Duration of use range in hours	Apgar<7 n (%)	NeoPuff or CPAP[1] (n (%)	Maternal moderate sedation n (%)
≤ 450	13 (40.6%)	1 - 4	1 (7.7%)	3 (23.1%)	0
451 to ≤900	11 (34.4%)	2 - 5	3 (27.3%)	4 (36.4%)	1 (9.1%)
901 to ≤1350	4 (12.5%)	6 - 7	1 (25.0%)	2 (50.0%)	0
1351 to <1800	2 (6.3%)	7 and 8	1 (50.0%)	1 (50.5%)	1 (50.0%)
1800	2 (6.3%)	10 and 14	0	0	1 (50.0%)
Total	32 (100%)	1 to 14	6 (18.8%)	10 (31.2%)	3 (9.4%)

1. CPAP: Continuous positive airway pressure

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