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Analgesia with sevoflurane during labour: I. Determination of the optimum concentration†‡

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Background. Sevoflurane has favourable physical qualities for inhaled analgesia during labour pain. The aim of this preliminary study was to identify its optimum concentration.

Methods. In this open-labelled escalating-dose study, 22 parturients in labour self-administered sevoflurane at 10 contractions using an Oxford Miniature Vaporiser. The inspired concentration was increased by 0.2% after each contraction from 0% to 1.4% or decreased if sedation occurred. Visual analogue scores (0–100 mm) for pain intensity, pain relief, sedation, mood and coping were measured after each contraction.

Results. The median (IQR [range]) pain relief and sedation scores increased from 44 (43–56 [4–93]) mm and 55 (43–56 [0–98]) mm at 0.2% sevoflurane, to 74 (72–78 [50–80]) mm and 71 (71–73 [33–97]) mm at 1.2% sevoflurane, respectively. Pain relief scores did not show any significant increase above 0.8% whilst sedation continued to increase, with excessive sedation occurring at 1.2% sevoflurane. No significant changes in other scores were measured.

Conclusions. We concluded that the optimal sevoflurane concentration in labour was 0.8%. This concentration allows a safety margin and balances the risk of sedation with the benefit of pain relief in labour.

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Sevoflurane is potentially an attractive inhalation agent for use as an analgesic during labour. Subanaesthetic concentrations offer advantages to mothers including a lack of irritation to the respiratory tract and a pleasant odour.[1–4] In addition, sevoflurane has a low blood-gas partition coefficient of 0.65 that enables rapid uptake into the central nervous system together with fast washout which results in swift clinical effect and recovery.[2]

The only agents with lower blood-gas partition coefficients are desflurane and nitrous oxide with values of 0.45 and 0.47, respectively. However, desflurane is pungent in character and may be associated with amnesic effects when used during childbirth.[5] Nitrous oxide, in the form of Entonox®, a 50:50 mixture with oxygen, is the standard inhaled analgesic available during labour in the United Kingdom. Entonox® is an effective and safe inhalation analgesic agent but has been the subject of criticism. We have therefore explored the use of sevoflurane as an alternative agent for use in labour.[6–10]

Sevoflurane is minimally metabolized in the body and preliminary work has proved its safety with both mother and baby.[1 11] A preliminary pilot study by Toscano and colleagues demonstrated successfully that sevoflurane can be used as an inhalation analgesic in labour.[1] This study administered sevoflurane in an intensive manner, with

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‡This article is accompanied by Editorial I.

parturients instructed to inhale MAC inspired concentrations just before each contraction and stop before that contraction had subsided to achieve end-tidal concentrations of 1–1.5%. Tight-fitting masks and large cumbersome equipment were required to achieve this and the authors admitted that their administration technique was impractical in the labour and there was no control or comparative group.

The aim of our pilot study was to determine the optimum inspired concentration of sevoflurane required for self-administered inhalation analgesia in a more practical setting than Toscano's, as a prelude to a comparison with Entonox in a subsequent study.

Methods

This open-label dose-escalating study received Local Research Ethics Committee approval. Women were recruited, with written consent, before labour in the antenatal classes or on the antenatal or delivery wards. As a result of the difficulty of truly informed consent during labour, only mothers who had been informed of the study before labour (i.e. the antenatal period) were allowed into the study. Inclusion criteria to participate in the study were for the parturient to be in established active labour (defined by the presence of $\geqslant$3 cm cervical dilation with contractions occurring at least once every 3 min either spontaneous or induced) gestation $\geqslant$36 weeks and with prior consent. Exclusion criteria included major uterine abnormalities, multiple gestation, cardiovascular or respiratory instability and acute or chronic obstetric pathologies such as pre-eclampsia. Women who had received any form of analgesia before recruitment were also excluded.

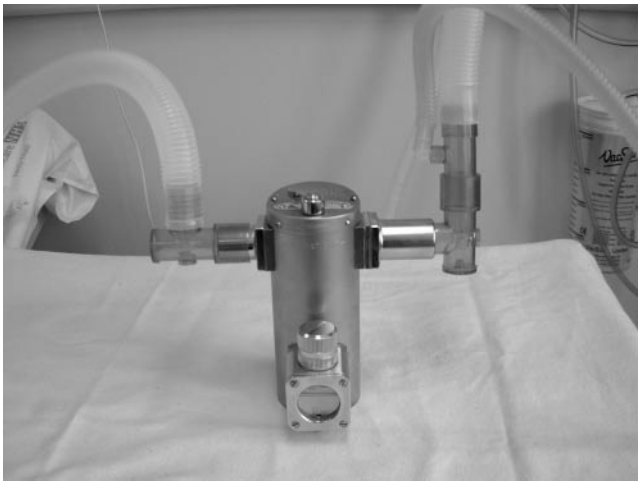

Fig 1 Sevoflurane was administered via a drawover Oxford Miniature Vaporiser (OMV; Penlon Ltd, Oxford, UK).

Sevoflurane was administered via a drawover Oxford Miniature Vaporiser (OMV; Penlon Ltd, Oxford, UK, Fig. 1). Half a metre of reservoir tubing (diameter 22 mm) was positioned at the inspiratory limb of the OMV to supply supplemental oxygen at 4 litre min^{-1} and the oxygen-enriched sevoflurane–air mixture was delivered through disposable corrugated tubing and a non-return valve to a heat-moisture exchanger (HME) and mouthpiece.

The primary outcome measure was the overall pain relief associated with each contraction. This and other outcome measures (pain intensity, sedation, mood and coping) were obtained using visual analogue scales (VAS) with 100 mm rulers bearing specific question and sliding markers (Table 1). Each VAS was performed between each of the 10 labour contractions studied. The use of VAS for pain relief, pain intensity, sedation and mood have been validated previously;[12–15] the VAS for coping was developed to assess further the beneficial properties of inhalation analgesia.[16] Inspired and expired gas concentrations (via a continuous sampling port connected to the HME) and maternal ventilatory frequency, intermittent non-invasive arterial pressure, heart rate and arterial oxygen saturation were measured with an AS/3 anaesthetic monitor (Datex Ohmeda, Hatfield, Herts, UK). Fetal heart rate and maternal contractions were monitored continuously using cardiotocography (CTG). Other measures included side-effects, type of analgesia used after the study, mode of delivery, estimated blood loss and neonatal Apgar scores.

Each participant started by breathing oxygen-enriched air alone for the first contraction and then the concentration of sevoflurane was increased by 0.2% for each subsequent contraction up to 1.4%. If the parturient experienced difficulty with the slide ruler, reading or comprehending the question, this was described as 'excessive sedation' and the sevoflurane concentration was reduced by 0.2% for the next contraction. Although a latin-square design is the more established method of determining drug dosage, we opted for a step-wise design, the reason being that we felt

Table 1 Questions used to measure outcomes during inhalation analgesia with sevoflurane during labour, using visual analogue scales, with the 0 and 100 mm anchor points

Outcome	Question	0 mm	100 mm
Pain relief	How much pain relief did you get through the last contraction?	'No relief'	'Complete relief'
Pain intensity	How painful was the last contraction?	'No pain'	'Worst possible pain'
Coping	How did you cope through the last contraction?	'Not at all'	'Coped well'
Mood	How do you feel?	'Best I could feel'	'Worst I could feel'
Sedation	How sleepy do you feel?	'Not sleepy at all'	'Almost asleep'

Table 2 Patients' characteristics and details of delivery after inhalation analgesia with sevoflurane during labour. Values are mean (SD [range]), number (proportion) or median (interquartile range [range]). *Including seven Caesarean sections and four assisted deliveries

Age; years	30 (5 [20–37])
Education (completed)	
School	2 (10%)
University	9 (45%)
Postgraduate	9 (45%)
Parity	
0	18 (90%)
1	2 (10%)
Labour	
Spontaneous	12 (60%)
Induced (no oxytocin infusion)	1 (5%)
Induced (oxytocin infusion)	7 (35%)
Delivery	
Spontaneous	9 (45%)
Assisted vaginal	4 (20%)
Caesarean section	7 (25%)
Estimated blood loss (ml)*	267 (133 [150–600])

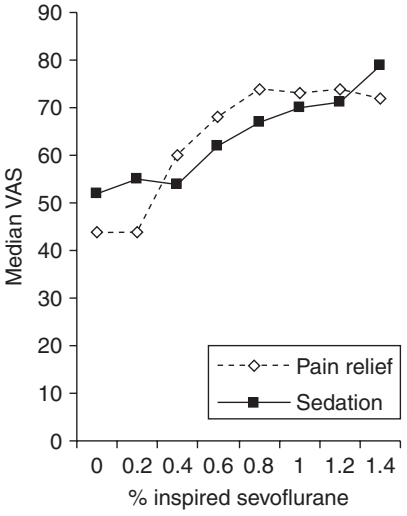

Fig 2 Median visual analogue scores for pain relief (diamond) and sedation (square) during inhalation analgesia with sevoflurane during labour. For clarity, IQR and range have been omitted (see text).

that sedation would be the limiting factor with the use of sevoflurane as an inhalation analgesic agent. In addition, when excessive sedation was observed the concentration was reduced.

Results

Of the 22 parturients recruited to the study all but two completed it. One parturient withdrew because she did not like the smell and the other requested epidural analgesia. Patients' characteristics and details of delivery are shown in Table 2. Of 20 parturients that participated in the study, each conducted five separate VAS (i.e. pain intensity, pain relief, sedation, mood and cope) between each contraction. A total of 695 VAS assessments were collected.

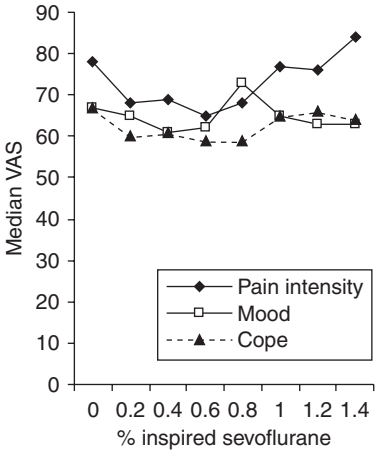

Fig 3 Median visual analogue scores for pain intensity (diamond), mood (square) and coping (triangle) during inhalation analgesia with sevoflurane during labour. For clarity, IQR and range have been omitted.

There was a dose dependent increase in median (IQR [range]) pain relief from 44 (43–56 [4–93]) mm at 0.2% sevoflurane to 74 (52–80 [23–97]) mm at 0.8%. However, there was no further increase in pain relief scores beyond 0.8% to 1.2% sevoflurane. Sedation scores increased from 55 (43–56 [0–98]) mm at 0.2% sevoflurane to 71 (71–73 [33–97]) mm at 1.2% (Fig. 2). No adverse events were observed apart from excessive sedation in four women (19%) at 1.2% sevoflurane and none experienced excessive sedation at 0.8% or 1.0%. There was no change in pain intensity, coping and mood with increasing sevoflurane (Fig. 3). There were no maternal adverse effects nor any adverse CTG changes observed. As a result of the physical characteristics of the drawover OMV, the inspired oxygen concentrations varied from 37% to 51% depending on inspiratory effort.

Discussion

Our results suggest that a concentration of sevoflurane of 0.8% was optimal for self-administered inhalation use during labour, based on the scores for pain relief and sedation. We anticipated that this would provide the best benefit to risk ratio and achieve maximal pain relief with minimum sedation. Interestingly, the VAS for pain intensity, mood and coping did not change with increasing sevoflurane concentrations.

This study was designed to measure pain relief but we included other measures so as to investigate the effects of inhalation analgesia during labour more comprehensively. A new addition was the 'coping' VAS.[12–15] We added this because the words 'coping' and 'cope' are frequently used during labour, by both the women and the staff. Behavioural pain psychologists consider that the locus of control is an important factor in pain management with a strong link

between 'control' and 'cope'.[16] To give a woman control allows her to manage her pain. Although in this study the results for this measure demonstrated no change, we have continued to investigate this score in subsequent trials.

As expected, a wide range was observed with all the VAS (pain intensity, pain relief, mood, sedation and 'coping'). Labour and its effect on each individual is extremely variable. This is a common difficulty when studying inhalation as opposed to neuroaxial analgesia in labour. A concern would be the variable efficacy of this technique. However, using a sequential increasing dose design with sedation being the ceiling point, we were able to achieve the optimum dose for safe, self-administered sevoflurane during labour.

We found improvements in pain relief scores without measurable improvements in pain intensity scores. In addition, median pain intensity score actually increases with inspired sevoflurane concentrations >0.8% (Fig. 4). We would presume that at subanaesthetic and subsedative levels of sevoflurane the quantifiable nature of pain intensity was not altered and therefore is independent of the study, thus increasing with the progression of labour. However, pain relief may be a more sensitive marker of analgesia, as it encompasses a broader description of the pain experience not exclusively limited to the quantity of pain felt (i.e. pain intensity). Another observation would be that sedation could be altering the perception of pain experienced. If that were so, pain intensity scores would decrease with increasing pain relief scores. Although this study does not determine the difference between effective analgesia and altered pain perception, we feel that the desired aim is still positive with increased pain relief scores.

Toscano showed that inspired concentrations of sevoflurane over 2% to achieve a target end-tidal concentration of 1–1.5% may alter pain intensity scores.[1] This technique would have been both impractical and dangerous with a self-administer technique. Significant sedative and possibly anaesthetic effects would have occurred at these higher concentrations. Even so, 4 of our 20 participants were unable to complete the VAS scores because of sedation at inspired concentrations of sevoflurane 1.2%.

A potential criticism of our study is the use of inspired sevoflurane concentrations as opposed to end-tidal concentrations. As a result of the low concentrations being studied and the intermittent administration of the agent to the labouring parturient, a steady state would never be achieved. Studies have shown that there are significant differences in alveolar (i.e. assumed to be end-tidal), inspiratory and arterial concentrations of inhalation anaesthetic agents, even when a steady state was achieved.[17 18] Therefore, we felt that our emphasis would be concentrated on effective receptor site action (i.e. VAS). We used the inspiratory concentration of sevoflurane as a guide to correlate with the VAS scores because delivering a set inspiratory concentration was more easily accomplished at these low concentrations than achieving a set end-tidal concentration. However, we did observe a steady difference of 0.2% between the inspired and expired sevoflurane concentration once regular respiration was established.

Achieving a fixed inspiratory concentration with the OMV was a challenge, as inspiratory effort alters the concentration of sevoflurane delivered. We felt that the advantages of the OMV of portability and small size outweighed its disadvantages. Each parturient was aided to establish a regular breathing pattern during each labour contraction by the midwives. This regular respiratory pattern established a constant inspired/expired sevoflurane concentration with the OMV. The alternative would have been the use of a high flow delivery sealed system, involving bulky equipment, a tight-fitting mask and larger volumes of sevoflurane.

Another challenge of studying parturients during normal labour is establishing at what point of the labouring process each parturient is at. Fortunately, all the parturients studied had recently received a vaginal examination (<1 h) and cervical dilation was >3 and <5 cm. Time data were not collected from the end of study to delivery which may have provided additional information on the progression of the labour, but again this is particularly variable in primigravidas.

Inhalation anaesthetic agents have been regularly used and studied during labour. This has been studied predominantly during the first stage of labour, and includes studies of enflurane 1% in air[19] and isoflurane 0.75%, or 0.2% in combination with Entonox.[20 21] Desflurane has only been studied in the second stage of labour, perhaps because of its pungency and lack of tolerability during early labour in contrast with the more intense and short-lived pains of the second stage.[5] Desflurane, administered at 1.0–4.5% with oxygen depending on the patients' requirements, provided comparable analgesia to Entonox but resulted in a 23% incidence of amnesia.[5]

Our preliminary study suggests that sevoflurane is both effective and acceptable in labour. Further, we have derived the inspired concentration that provides the best risk-to-benefit ratio.

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