Cough reflex sensitivity after elective Caesarean section under spinal anaesthesia and after vaginal delivery

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Background. In pregnancy, airway oedema and heartburn may increase cough sensitivity, whereas spinal anaesthesia (SA) with local anaesthetics and opiates may decrease it. Decreased cough sensitivity increases the risk for pneumonia or retained secretions. The aim of this study was to determine whether cough sensitivity is increased in pregnant patients and if it is decreased after planned Caesarean section (CS) under SA.

Methods. Twenty-seven non-pregnant volunteers, 27 patients after vaginal delivery (VD group), and 28 patients after CS under SA (CS group) were studied. For SA, hyperbaric bupivacaine 8–12 mg, sufentanil 5 μg, and morphine 100 μg was given. Increasing concentrations of nebulized citric acid were delivered until eliciting cough. The concentration eliciting one (C1) and two coughs (C2) were recorded and log transformed for analysis (log C1 and log C2).

Results. Median (inter-quartile) log C1 was 1.3 (0.6) mg ml⁻¹ in the VD group, 1.6 (0.6) mg ml⁻¹ in the non-pregnant group (P<0.01 vs VD group), and 2.2 (0.7) mg ml⁻¹ in the CS group (P<0.0001 and P<0.01 vs VD and non-pregnant groups, respectively). Similar results were observed with log C2. In CS group, log C1 and log C2 remained increased up to 4 h after SA.

Conclusions. Cough sensitivity was increased after VD but decreased for up to 4 h after SA.

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Current spinal anaesthesia (SA) technique for Caesarean section (CS) uses a combination of local anaesthetic, short-acting lipophilic opiate (fentanyl or sufentanil), and small-dose morphine. Use of opiates allows for a reduction in local anaesthetic requirement and postoperative analgesia. Concerns have been expressed for intrathecal opiate administration, especially morphine. Indeed, intrathecal morphine in dose as small as 200 μg can depress the ventilatory response to carbon dioxide for up to 24 h. This might potentially place patients at risk for respiratory adverse events.

Apart from blunting the ventilatory response to carbon dioxide, systemic opiates can depress the sensitivity of lung protective reflexes, such as cough reflex. Moreover, systemic and inhaled local anaesthetics can also impair the sensitivity of upper airway reflexes. However, the effects of intrathecal opiates and local anaesthetics on cough reflex sensitivity have not been investigated. Previous studies have reported that impaired cough reflex sensitivity can be a risk factor for pneumonia or retained secretions; hence, impaired cough reflex sensitivity after SA may contribute to their occurrence during or after surgery. Nevertheless, changes associated with pregnancy may have a protective effect from SA-induced cough sensitivity impairment. Indeed, upper airway capillary engorgement and oedema and gastro-oesophageal reflux are responsible...
for enhanced airway reactivity and increased cough sensitivity, respectively.\textsuperscript{8–10}

We have conducted this study to determine, first, whether cough reflex sensitivity is increased in pregnant patients compared with non-pregnant patients and, secondly, whether cough sensitivity is decreased after planned CS under SA with bupivacaine, morphine, and sufentanil compared with pregnant and non-pregnant patients.

\section*{Methods}

This study was conducted in the Obstetrics Department of Bichat University Hospital between December 2004 and June 2006. It was approved by the Ethics Committee for Protection of Patients of Hôtel-Dieu Hospital, Assistance Publique-Hôpitaux de Paris, Paris.

During the obligatory pre-anaesthetic examination between 34 and 36 weeks of amenorrhoea, patients were informed that they could be approached during their hospital stay for participating in a clinical study. This information was repeated in the information leaflet about hospitalization in our institution. The written informed consent was obtained on the first morning after vaginal delivery in the vaginal delivery group and on the morning of surgery in the CS group.

Three groups of female patients were studied. The first group included 27 healthy non-pregnant volunteers. The second group comprised 27 patients after uneventful vaginal delivery. All of the parturients had undergone epidural analgesia with continuous infusion of bupivacaine 0.1% and sufentanil 0.4 \textmu g ml\textsuperscript{-1}. Infusion was stopped after the delivery. The third group comprised 28 patients after elective CS under SA. SA was performed at the L3–L4 or L4–L5 interspaces in the sitting position with a 25-gauge pencil-point needle. A combination of hyperbaric bupivacaine 0.5\%, 8–12 mg, sufentanil 5 \textmu g, and preservative-free morphine 100 \textmu g was injected over more than 60 s in a volume ranging from 3.8 to 4.2 ml. Bupivacaine dose was selected according to patient’s height: 8–10 mg for height between 150 and 160 cm, 10–12 mg for between 160 and 170 cm, and 12 mg for above 170 cm. For postoperative analgesia, a combination of i.v. acetaminophen (1 g every 6 h) and ketoprofene (100 mg every 12 h) was used. If these analgesics did not relieve pain, morphine 5 mg s.c. was administered.

The following were the exclusion criteria: breast-feeding, age $>40$ yr, instrumental delivery, systemic opiates administration $<12$ h before the cough challenge, active smoking (smoking had to be stopped for at least 1 yr), diabetes mellitus, hypertension, chronic cough or chronic respiratory disease, allergic rhinitis, respiratory tract or upper airway infection during the last month, usual medication with psychotrops (anxiolytic and anti-depressive medications) or with angiotensin-II receptor inhibitor, pharyngolaryngeal disease, and neurological disorder.

Cough reflex sensitivity was measured using citric acid. Increasing concentrations of nebulized citric acid (2.5, 5, 10, 20, 40, 80, 160, 320, and 640 mg ml\textsuperscript{-1}) were delivered during inspiration until cough was elicited.\textsuperscript{11,12} The order of administration of citric acid solutions was always the same, from the lowest to the highest concentration. The concentrations eliciting one cough (C1) and then eliciting two coughs (C2) were recorded. All challenges were conducted by the same investigator. An independent observer counted the number of coughs elicited. If cough was not evoked with the highest concentration tested (640 mg ml\textsuperscript{-1}), C1 and C2 were arbitrarily set at 1280 mg ml\textsuperscript{-1}. C1 and C2 were log transformed for statistical analysis (log C1 and log C2).

During the cough challenge, the patient was sitting and wore a nose-clip. The patient was asked to exhale to functional residual capacity and then inhale to total lung capacity at a constant speed through a mouthpiece (single-breath inhalation technique). For a start, the 2.5 mg ml\textsuperscript{-1} citric acid solution was nebulized during one respiratory cycle. If cough was not evoked, the higher concentration was administered. The concentration was doubled until eliciting cough. Twice during the test, citric acid was replaced by saline to minimize patient’s adaptation. A jet breath-activated nebulizer was used (Nebulizer dosimeter ATOMISOR NL11D\textsuperscript{®}, La Diffusion Technique Française, Saint-Etienne, France). At each breath 8 \mu l of solution were nebulized. Citric acid solution was prepared by the Hospital Pharmacy. Citric acid powder was diluted in saline.

In a previous study of 15 healthy non-smoker patients, the difference between two log C1 measurements performed on the same day in the same patient was 0.12 (0.30) mg ml\textsuperscript{-1} [mean (sd)] or 0.0 (0.30) [median (inter-quartile)].\textsuperscript{13}

In the control group, the test was performed once in the morning before midday, as the threshold is known to increase during the afternoon.\textsuperscript{14} In the vaginal delivery group, the test was performed once, the first morning after delivery. The median time (inter-quartile) elapsed between vaginal delivery and cough challenge was 14 (8) h. In the CS group, the test was performed as soon as possible after arrival in the post-anaesthesia care unit (PACU). The median time (inter-quartile) elapsed between SA and cough challenge was 2.0 (0.6) h. In 13 patients, the test was repeated 4 and 24 h after spinal puncture.

Before each cough challenge in CS patients, motor blockade was assessed by the same investigator with the modified Bromage score and the height of sensory anaesthesia measured with an alcohol swab was recorded.\textsuperscript{15}

Patients’ characteristics, log C1, and log C2 in the three groups were described using median (inter-quartile) and median (extreme value) for dermatomal level. They were compared simultaneously across the three groups using...
Results

The characteristics of the three groups are presented in Table 1. Control group has significantly lower weight than vaginal delivery and CS groups and was younger than the CS group. In the CS group, one patient received 8 mg of hyperbaric bupivacaine, one patient 9 mg, 15 patients 10 mg, one patient 11 mg, and 10 patients 12 mg.

The cough reflex threshold assessed by log C1 to citric acid was 1.3 (0.6) mg ml$^{-1}$ in the vaginal delivery group, 1.6 (0.6) mg ml$^{-1}$ in the non-pregnant group and 2.2 (0.7) mg ml$^{-1}$ in the CS group (Fig. 1). Log C1 was significantly higher in the non-pregnant group than in the vaginal delivery group ($P<0.01$) and in the CS group than in the vaginal delivery and non-pregnant groups ($P<0.0001$ and $P<0.01$, respectively). Log C2 to citric acid was 1.6 (0.6) mg ml$^{-1}$ in the vaginal delivery group, 1.7 (0.3) mg ml$^{-1}$ in the non-pregnant group, and 2.2 (0.6) mg ml$^{-1}$ in the CS group. Log C2 was significantly higher in the non-pregnant group than in the vaginal delivery group ($P=0.015$) and in the CS group than in the vaginal delivery and non-pregnant groups ($P<0.0001$ and $P<0.001$, respectively).

Table 1 Clinical characteristics of the three groups of female patients; results are expressed as median (inter-quartile) or median (extreme value) for dermatomal level or mean (range) for age and mean (SD) for height; PACU, post-anaesthesia care unit; *$P<0.016$ vs non-pregnant group; **$P<0.016$ vs vaginal delivery group. 1Body mass index is calculated with the weight measured before vaginal delivery or CS. †1: no movement of the lower extremities; 2: able to flex ankles; 3: able to flex knees; 4: able to flex hips in the supine position; 5: able to stand; 6: able to stand and do a partial knee bend. 15

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant ($n=27$)</th>
<th>Vaginal delivery ($n=27$)</th>
<th>Caesarean section ($n=28$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>26 (18–38)</td>
<td>29 (16–39)</td>
<td>32 (23–41)*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 (4)</td>
<td>163 (6)</td>
<td>163 (8)</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)$^1$</td>
<td>20.9 (2.8)</td>
<td>25.9 (6.2)$^*$</td>
<td>28.2 (6.7)$^*$</td>
</tr>
<tr>
<td>Pregnancy term (weeks of amenorrhea)</td>
<td>—</td>
<td>39 (2)</td>
<td>38 (3)**</td>
</tr>
<tr>
<td>Modified Bromage score on arrival in PACU$^3$</td>
<td>—</td>
<td>—</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Height of sensory anaesthesia to cold on arrival in PACU</td>
<td>—</td>
<td>—</td>
<td>D6 (L1–C2)</td>
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</tbody>
</table>

Thirteen patients in the CS group underwent three cough challenges. Five patients received 5 mg s.c. morphine 13 (2) h before the third challenge. Evolution of the modified Bromage score and of the height of anaesthesia to cold in these 13 patients is presented in Table 2. Log C1 to citric acid was 2.5 (0.4) mg ml$^{-1}$, 2.2 (0.6) mg ml$^{-1}$, and 1.9 (1.0) mg ml$^{-1}$ on arrival in the PACU, 4 and 24 h, respectively, after spinal puncture. Individual values are presented in Figure 2. Log C1 values at arrival to PACU and at 4 h were not significantly different ($P=0.091$), but at 24 h, the values were significantly lower ($P<0.01$ compared with the preceding two measurements). Similar results were observed with log C2.

Discussion

In this prospective study, we have shown, first, increased cough sensitivity to citric acid early after vaginal delivery...
We also observed decreased cough sensitivity in the CS group on arrival in the PACU, 2 h after spinal injection, compared with vaginal delivery and non-pregnant groups. Both opiates and local anaesthetics may account for this result since both drugs are cough depressants. Decreased cough sensitivity to capsaicin is observed as early as 15 min after 0.15 mg kg\(^{-1}\) i.v. morphine injection.\(^3\) Moreover, cough elicited by mechanical stimulation of the trachea is abolished after 1.5 mg kg\(^{-1}\) i.v. lidocaine as long as its blood concentration is more than 2.3 \(\mu g mL^{-1}\).\(^4,5\) Similar results have been reported in animals after inhaled bupivacaine.\(^5\) As we did not study separately the effect of bupivacaine, sufentanil, and morphine on cough sensitivity, we cannot draw any final conclusion about the mechanism responsible for the decreased sensitivity that we measured on arrival in the PACU. However, cough sensitivity impairment was long lasting up to the fourth hour after spinal injection, which may suggest a responsible mechanism. At that time, the effect of bupivacaine had almost vanished as illustrated by an almost normal Bromage modified score. Therefore, long-lasting cough depression was probably linked to the opiates and most likely to morphine. Indeed, the effect of small dose intrathecal sufentanil would be expected to be short lasting. As demonstrated by Standl and colleagues,\(^23\) blood and cerebrospinal fluid sufentanil concentrations were undetectable 2 h after 5 \(\mu g\) spinal injection. In addition, the effect of higher intrathecal sufentanil dose (12.5 \(\mu g\)) on the ventilatory response to carbon dioxide had disappeared by 2 h.\(^24\) Moreover, the results of studies of such low-dose intrathecal morphine on other respiratory functions may support the involvement of morphine. For example, 200 \(\mu g\) intrathecal morphine depressed the ventilatory response to carbon dioxide for up to 24 h with a time to peak effect of 3.5 h.\(^7\) Similarly, the ventilatory response to hypoxia was depressed after 300 \(\mu g\) intrathecal morphine with a magnitude similar to that after the administration of 0.14 mg kg\(^{-1}\) i.v. morphine.\(^25\) S.C. morphine administration to five patients of the CS group before the third cough challenge may have influenced the results, as morphine increases log C1 and log C2.\(^3\) However, we observed a decrease in log C1 and in log C2 at that time rather than an increase, suggesting that morphine administration had minimally influenced the results of the third test.

To the best of our knowledge, only one study has so far examined the safety of SA with small-dose morphine for CS.\(^26\) In a cohort of 800 patients, Abouleish and colleagues did not report any serious adverse respiratory events during the first 24 h after CS under SA, including 200 \(\mu g\) morphine. These results might suggest a safe practice. However, the rate of respiratory complications associated with SA is low.\(^27–29\) For example, Arozullah and colleagues have reported 272 cases of pneumonia after major non-cardiac surgery under SA in a cohort of 30534 patients (0.9%).\(^29\) Therefore, the study by Abouleish and colleagues could not have the sample size to pick up
respiratory complications. The results of the current study demonstrate that the afferent pathway of cough reflex is impaired after SA. Therefore, patients undergoing CS under SA may be at risk for aspiration or retained secretions during and after surgery. Indeed, several studies have demonstrated a link between decreased cough sensitivity and risk of aspiration pneumonia or retained secretions. Also decreased cough sensitivity has been reported in patients with high risk of postoperative respiratory complications such as smokers, diabetic, or elderly patients. In addition, decreased cough sensitivity is observed in medical patients with aspiration pneumonia or recurrent pneumonia. During surgery, the risk of aspiration may further be increased by surgical abdominal manipulations. Hartsilver and colleagues reported a 50% increase in gastric pressure during CS. As the impairment of cough sensitivity observed in the current study may extend beyond the fourth hour, the risk may persist after surgery.

In conclusion, increased cough sensitivity was observed after vaginal delivery, whereas it was decreased up to the fourth hour after SA with bupivacaine, sufentanil, and morphine.

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