OBSTETRICS

Duration of analgesia and pruritus following intrathecal fentanyl for labour analgesia: no significant effect of A118G μ-opioid receptor polymorphism, but a marked effect of ethnically distinct hospital populations

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Background. Genetic polymorphism (A118G) in the μ-opioid receptor has been reported to affect systemic opioid analgesia. However, reported pharmacogenetic effects on spinal opioid analgesia, particularly in labour, have been equivocal.

Methods. We prospectively assessed effects of the μ-opioid receptor A118G single nucleotide polymorphism (SNP) on analgesia after 20 μg of spinal fentanyl. We studied two ethnically distinct hospital populations (Miami and Jerusalem). Independent variables were A118G, ethnicity, and hospital. Primary outcome was time from spinal analgesia until analgesic request. Secondary outcomes were pain and pruritus, assessed at repeated intervals until analgesia request.

Results. One hundred and twenty-five nulliparous parturients in early labour were analysed. The allelic frequency of A118G was 14.8% (14.4% in Miami; 15.5% in Jerusalem). Time to analgesia request (SD) in Miami was 122 (44) min and in Jerusalem was 87 (32) min, P < 0.001; Hispanic 123 (46) min vs Jew/Arab 87 (32) min, P < 0.001; Black 121 (41) min vs Jew/Arab 87 (32) min, P = 0.015. There was no significant effect of A118G. Survival analysis showed Miami > Jerusalem, P < 0.001; Hispanics and Black > Jew/Arab, P < 0.001; no effect of A118G. Within hospital groups, A118G had no effect on time to analgesic request; within genomic groups there was a significant difference between hospitals. The time-course for pruritus exactly paralleled the time-course for analgesia and was affected by hospital (P = 0.006) and by ethnic group (P = 0.03), but not by A118G.

Conclusions. We found no significant effect for the A118G single nucleotide polymorphism (SNP) on analgesic duration after spinal fentanyl for labour. In contrast, ethnically distinct hospital population groups exerted a marked effect on the time-course of both analgesia and pruritus.

Keywords: analgesia, obstetric; analgesics opioid, fentanyl; genetic factors.

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There are wide inter-individual differences in the perceived pain of labour and the response to analgesic medication, largely attributed to maternal-fetal factors. Individual differences in pain perception and analgesic response have also been associated with genomic variables1,2 which can affect drug bioavailability3 and the structure of target receptors.4 One of the important targets for receptor pharmacogenetic studies in pain research has been the μ-opioid receptor (MOR), encoded by the opioid receptor, μ 1 gene (OPRM1).

The most commonly occurring SNP for OPRM1 is a substitution of adenine by guanine at nucleotide position 118 (A118G).1,5 There have been contrasting findings regarding the impact of A118G on pain and analgesia. Early studies suggested that A118G is protective against pain,5 being associated with an increased pain threshold to experimental pressure and heat pain in female volunteers.6 However, subsequent studies reported that A118G reduces opioid analgesic response and increases opioid requirement in patients with acute pain,7

Editor’s points

- Genetic polymorphism in the μ-opioid receptor can affect systemic opioid analgesia.
- The effects of the A118G polymorphism on analgesia and pruritus after intrathecal fentanyl for labour analgesia were compared in two ethnically distinct populations.
- While there was no effect of the genetic polymorphism, there was a marked effect of the ethnically distinct groups on duration of both analgesia and pruritus because of other factors.
chronic pain, and experimental pain and also reduces other opioid-mediated effects, such as pupil constriction, particularly in homozygous (GG) patients. Although a meta-analysis found no consistent association between A118G and pain phenotypes, additional studies performed since that meta-analysis have consistently demonstrated that A118G is associated with poor analgesic response to opioids. Humanized mice homozygous for A118G demonstrated reduced analgesic effect compared with wild-type controls. Different in vitro models have demonstrated that A118G is associated with a reduction in allele-specific mRNA, MOR protein expression, and opioid binding affinity to MOR, although the number of MOR binding sites was unaffected.

We recently demonstrated an increased systemic opioid requirement for i.v. alfentanil patient controlled analgesia (PCA) in patients with A118G, who self-administered a higher dose, achieved higher plasma drug concentration, and yet complained of more severe pain. Our aim in the current study was to assess the effect of A118G on the action of an intrathecal opioid acting at spinal cord opioid receptors. Four recent studies of spinal opioids in obstetric patients have demonstrated diverse findings. Two studies directly assessed the potency of spinal opioids and found that A118G was associated with higher potency for spinal fentanyl and epidural sufentanil for labour analgesia. Conversely, Sia and colleagues reported that A118G was associated with increased i.v. PCA morphine requirements after spinal morphine for Caesarean delivery. Finally, Wong and colleagues found no effect of A118G on analgesic duration after spinal fentanyl for labour analgesia or spinal morphine for Caesarean delivery.

We designed a prospective observational pharmacodynamic study to assess the effect of A118G on analgesia after a single spinal dose of fentanyl among women receiving combined spinal epidural analgesia in early labour (2–5 cm dilation). These women initially only received spinal fentanyl and repeated observations were made until the request for additional analgesia was administered via the epidural catheter. In accordance with our previous study suggesting reduced potency for opioids in A118G, we hypothesized that A118G (either homozygotes GG, or heterozygotes AG) will require supplemental epidural analgesia sooner after the spinal dose than wild-type (AA) controls. As demographic heterogeneity is advantageous in pharmacogenetic studies, we assessed this hypothesis simultaneously in two large tertiary medical centres, in Miami and Jerusalem, each with its own distinct heterogeneous ethnic population.

Methods

Subjects

The Institutional Review Boards of both Hadassah Hebrew University Medical Center and the University of Miami Miller School of Medicine approved this observational research study performed in 2006, and all subjects signed informed consent. Patients were eligible if they were nulliparous, age 18–40, in early labour (cervical dilatation 2–5 cm), ASA status I–II, body weight ≤ 110 kg, gestational age > 36 weeks, with a singleton pregnancy in vertex presentation. Patients were excluded if they received any opioid in the previous 3 h, had a history of chronic pain medication use or substance abuse, had obstetric risk factors (previous uterine surgery, gestational diabetes mellitus, macrosomia, or pre-eclampsia), or were unable to understand the consent form.

The following demographic variables and obstetric risk factors were recorded upon enrolment in the study: age, height, weight, ethnic origin of both parents of the parturient, cervical dilatation at enrolment into the study, gestational age, induction or augmentation of labour, premature rupture of membranes (PROM), and artificial rupture of membranes (AROM). The following obstetric outcome variables were recorded after delivery: duration of the first and second stages of labour, newborn weight, instrumental delivery, and Caesarean delivery.

Blinding

As DNA assays were performed after labour analgesia and after obtaining all clinical data, the investigator enrolling subjects and recording data was unaware of the genomic group; it was clearly not possible to achieve blinding to ethnicity or hospital. The technician performing the DNA assay was blinded to all clinical and demographic data.

Spinal analgesia

Combined spinal epidural (CSE) analgesia was performed using an 18G Tuohy epidural needle (Hadassah: 18G 8 cm, BBraun Medical, Inc., Melsungen, Germany; Miami: 18G 9 cm, BBraun, Medical, Inc., Bethlehem, PA, USA) or what was assumed to be the L3/4 or L4/5 interspace using loss of resistance to air in the sitting position with the needle through needle technique. A 26G atrumatic spinal needle (Hadassah and Miami: 26G 12.4 cm, Gertie Marx needle, IMD, Inc., Huntsville, UT, USA) was inserted past the tip of the Tuohy needle until it was felt to pass the dura. Intrathecal placement was confirmed by flow of cerebrospinal fluid (CSF) either spontaneously or on aspiration into a 2 ml syringe. Fentanyl 20 μg (50 μg ml⁻¹; Hadassah: Janssen-Cilag, Beeser, Belgium; Miami: Baxter Healthcare Corp., Deerfield, IL, USA) was administered intrathecally with no local anaesthetic or adjuvant drug using a 1 ml syringe followed by 1 ml of preservative-free saline, by slow injection more than ~5 s. A 19G epidural catheter was then inserted 3–5 cm into the epidural space.

Withdrawal criteria

Subjects were withdrawn from analysis if there were technical complications with the CSE (inadvertent spinal placement of Tuohy needle, inability to aspirate CSF via spinal needle either before or after spinal drug administration), if the visual analogue pain score (VAPS) was ≥ 20 mm at 20 min after spinal drug administration, or if the subject progressed to either vaginal or operative delivery before analgesic request.
Measurements

Observations were recorded by an investigator who was present by the bedside or in the immediate vicinity throughout the study. The primary outcome was the time until first request for additional analgesia from the time of spinal drug administration. Continuous data (see below) were recorded during peak uterine contraction at the following time points: (i) the three contractions before spinal analgesia, (ii) the first five contractions after spinal analgesia, (iii) the first contraction that followed each subsequent 15 min interval, and (iv) the first request for additional analgesia. After first analgesic request, all subjects received incremental epidural doses of bupivacaine 0.1% with 2 μg ml⁻¹ fentanyl to achieve analgesia, and were then treated with epidural PCA using the same solution.

We recorded the time from spinal analgesia to first request for additional analgesia. VAPS was assessed at each of the time points above using an ungraduated linear 0–100 mm ruler, with 0=no pain and 100=worst pain imaginable.

We also recorded heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), pruritus, and nausea at each of the time points. Pruritus and nausea were rated separately using visual analogue scale (VAS) as described above, with 0=no symptom and 100=worst symptom imaginable.

Genotyping

Venous blood (5 ml) was sampled at the time of enrolment. DNA was extracted from peripheral leucocytes using a traditional salting out extraction procedure. Identification of MOR polymorphisms at codon 40 (Asn40Asp) was performed by polymerase chain reaction (PCR) followed by digestion with restriction enzymes. Using the forward primers 5’-CGGTTCTGGGTCAACCTGCCCACCTTAGATCGC-3’ and the reverse primer 5’-AGCCTGGGAGTTAGGTGTCC-3’, a 298 bp DNA fragment was amplified (Roche LightCycler). The PCR programme consisted of initial denaturation at 94 °C for 2 min followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 67 °C for 45 s, and extension at 72 °C for 45 s, plus a final extension at 72 °C for 7 min. The amplified DNA fragment was incubated for 4 h with BstUI restriction enzyme at 60 °C, as described. The digested products were separated in 3% agarose gel, and visualized by ethidium bromide staining.

Statistical analysis

The primary end point was the time from spinal fentanyl to first request for additional analgesia. Secondary end points were: VAPS, pruritus, nausea, and MAP. We assessed the effects of the following independent variables: A118G (AA or AG/GG), ethnic group and hospital (Miami or Jerusalem). Data are presented as mean (SD) or counts (%) where appropriate. Data were assessed for normal distribution. The time to analgesic request was assessed using survival analysis (Kaplan–Meier curves and Cox regression analysis); difference between means was assessed by one-way analysis of variance (ANOVA) (with Bonferroni post hoc test when comparing three groups). The effects of time on VAPS, VAS severity of pruritus and nausea, and MAP were assessed by repeated measures (RM) ANOVA (RM-ANOVA) with polynomial contrast; aforementioned independent variables were between-subject factors. The incidence of pruritus (binary outcome: VAS ≤ 20 mm or VAS > 20 mm) as a function of time was assessed using generalized estimating equations (GEE) in a generalized linear model for RM. Binary demographic and outcome data were assessed by exact χ² test. All P-values were two-tailed; statistical significance was assumed at P < 0.05; statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA and SAS 9.3, SAS Institute, Inc., Cary, NC, USA).

Sample size calculation

Mean and (so) for sample size estimations were based on published data for the duration of 20 μg intrathecal fentanyl for labour analgesia [92 (34) min23]. In order to demonstrate a 30 min (33%) difference in the time to request additional analgesia between two groups with 91% power and P=0.05, 26 subjects are necessary in each group. Based on an estimated prevalence in the population of A118G of 20%,1 we calculated a need to enrol 124 subjects.

Results

Subjects

Subjects included 137 nulliparous women in early labour; 12 were excluded from final analysis, 3 because of technical failure to extract DNA, 3 because of rapid progress to vaginal or operative delivery before the request for additional analgesia, 2 because of inability to aspirate CSF, and 4 because of VAPS remaining > 20 mm after 20 min after the spinal (2 each at Miami and Jerusalem). Two of the 4 subjects who were rejected because of inadequate analgesia

| Table 1 | Distribution of MOR A118G between ethnic groups and hospital. Data expressed as counts (% of the ethnic or hospital subgroups) and analysed by Fisher’s exact test (some of the cells have expected values < 5). There was a significant effect of ethnicity on the distribution of A118G: AA vs AG/GG, P = 0.018, largely driven by the fact that all 17 Blacks were AA. ‘Others’ removed from analysis because of small sample size. Hospital population: there were no distributional differences between hospitals; AA vs AG/GG, P = 0.923 |
|----------------|----------------|------------|------------|------------|
| Ethnicity      | Total (n = 125) | AA (n = 91) | AG (n = 31) | GG (n = 3) |
| Jew/Arab       | 45 | 31 (69%) | 12 (27%) | 2 (4%) |
| Black          | 17 | 17 (100%) | 0 (0%) | 0 (0%) |
| Hispanic       | 60 | 39 (65%) | 19 (32%) | 2 (3%) |
| Others         | 3  | 3 (100%) | 0 (0%) | 0 (0%) |
| Hospital       |    |           |           |            |
| Miami          | 80 | 59 (74%) | 19 (24%) | 2 (2%) |
| Jerusalem      | 45 | 32 (71%) | 12 (27%) | 1 (2%) |
(Jerusalem) had blood sent for genotyping; of these, one was GG and one AA. There were no demographic differences between excluded and analysed subjects. As this was an observational study, intention to treat analysis was inappropriate.

Of the remaining 125 subjects 91 were AA (59, Miami, 32 Jerusalem), 31 were AG (19 Miami, 12 Jerusalem), and 3 were GG (2 Miami, 1 Jerusalem) (Table 1). The allelic frequency of A118G in the study population was 14.8% (14.4% in Miami and 15.5% in Jerusalem). The frequency of AA, AG, and GG subjects in our population was in Hardy–Weinberg equilibrium. There was no significant difference in the distribution of the A118G between the two centres.

**Analgesia**

Time to first request for additional analgesia, the primary endpoint, is presented in Table 2 together with the corresponding V APS. The time to analgesic request was significantly different between hospital groups; Miami 122 (44) min compared with Jerusalem 87 (32) min (P<0.001), with similar differences between the ethnic groups in Miami and the ethnic groups in Jerusalem. There was no effect of A118G.

There was a predictable within-subjects time relationship for the reduction in V APS over the first five uterine contractions after spinal analgesia (Fig. 1). However, there was no significant difference detected between groups. There was a significant effect of hospital (P<0.001) on the time-course of analgesia offset, but no effect of A118G.

A clear illustration of the marked difference between the ethnic/hospital groups together with the lack of difference between the genomic groups is shown in Kaplan–Meier survival curves for the time until request for supplemental analgesia after spinal fentanyl (Fig. 3). The survival curves for AA and AG/GG were almost identical (P=1.0), however there was a significant difference between Miami and Jerusalem (P<0.001) and between the ethnic groups in Miami and Jerusalem. Within the hospital subgroups, A118G had no effect on time to analgesic request. Within each genomic group there was a significant difference between hospitals.

As all the Hispanic and Black subjects were at Miami, and all the Jews and Arabs were at Jerusalem, it is not possible to assess from these data whether the differences are attributable to ethnicity or hospital. However, A118G had no clinically relevant effect on time to analgesia request.

Neither the use of oxytocin (based on Jerusalem data; Supplementary Fig. S1) nor baseline haemodynamic parameters (Supplementary Fig. S2) affected the time to analgesic request. The mean V APS at request for analgesia was remarkably similar between populations (Supplementary Fig. S3). Interestingly, the three GG patients requested analgesia earlier (87 min) and at a lower V APS (34 mm) (Supplementary Fig. S3); however these few subjects cannot be analysed statistically.

**Table 2**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Ethnicity</th>
<th>Hospital Site</th>
<th>Time to request for analgesia (min)</th>
<th>V APS at request for analgesia (0–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA (n=91)</td>
<td>Jew/Arab</td>
<td>Miami (n=80)</td>
<td>110.1 (41.5)</td>
<td>57.6 (17.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jerusalem (n=45)</td>
<td>108.3 (48.8)</td>
<td>55.0 (17.4)</td>
</tr>
<tr>
<td>AG/GG (n=34)</td>
<td>Hispanic</td>
<td>Miami (n=60)</td>
<td>120.6 (41.2)</td>
<td>57.1 (12.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jerusalem (n=43)</td>
<td>123.4 (46.2)</td>
<td>54.9 (20.5)</td>
</tr>
<tr>
<td></td>
<td>Black (n=17)</td>
<td>Miami (n=17)</td>
<td>87.3 (32.1)</td>
<td>61.8 (16.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jerusalem (n=3)</td>
<td>91.4 (20.5)</td>
<td>77.1 (12.9)</td>
</tr>
</tbody>
</table>

Time to request for analgesia was similar between all populations analysed. The interaction between genotype and ethnicity (Jew/Arab vs Hispanic) was not significant for either time to analgesic request (P=0.071) or for V APS at analgesia request (P=0.959). Blocks were not analysed in ethnic/genotype interactions, as all Blacks were AA genotype.
Duration of analgesia and pruritus following intrathecal fentanyl

Side-effects

There were no significant haemodynamic differences between groups. The effects of genomic, ethnic, and hospital groups on pruritus are presented in Figure 4. Overall, 79% of subjects complained of significant pruritus (≥20 mm VAS) with average maximum pruritus VAS 36 mm and time to maximum (Tmax) 15 min. The onset and offset of pruritus exactly paralleled the time-course of analgesia as described above. The maximum pruritus VAS and Tmax were not affected by genomic, ethnic, or hospital group. The diminution over time of pruritus severity (VAS) was affected by hospital (Jerusalem faster improvement than Miami, P=0.006) and by ethnic group (Jew/Arab faster improvement than Blacks and Hispanics, P=0.03), while there was no effect of genotype. Similarly, the incidence over time of significant pruritus (pruritus ≥20 mm VAS) was affected by hospital (Jerusalem faster improvement than Miami, P<0.001) and by ethnic group (Jew/Arab faster improvement than Blacks and Hispanics, P<0.001), while there was no effect of genotype.

Subject characteristics, obstetric risk factors, and obstetric outcome

Subject characteristics (Table 3) and obstetric outcome data (Table 4) are compared by genetic, ethnic, and hospital groups. There were no significant effects of genetic group. There were differences between ethnic groups and hospital groups which likely reflect the discrete ethnic characteristics of the two hospital populations. Maternal weight was higher and maternal height was lower in Miami. Miami had a 43% Caesarean delivery rate in enroled patients, as compared with 9% in Jerusalem. Cervical dilatation before spinal analgesia was on average 0.8 cm greater in Miami.

Discussion

Lack of effect of A118G

In our previous study of PCA alfentanil for procedural pain, we demonstrated a marked (≥50%) increase in systemic opioid requirement and pain severity for the MOR A118G (AG/GG combined compared with AA genetic polymorphism). In the current study, in the same ethnic population and for the same AG/GG vs AA comparison, we did not observe a significant effect of MOR A118G on spinal fentanyl duration, despite the clinical model having sufficient power to identify clear differences between ethnic/hospital groups. These findings are in accord with those of Wong and colleagues21 who also found no effect of A118G on analgesic duration after spinal fentanyl.

Several factors might explain this negative finding:

Spinal compared with systemic opioid administration: opioid pharmacodynamic effects could be less predictable for spinal administration when compared with systemic administration, as effect-site opioid concentrations are affected by CSF volume, speed and volume of injection, baricity, and lipophilicity.

Use of analgesic duration as an effect measure: although analgesic duration is widely used as a pharmacodynamic endpoint in spinal analgesia,18 21 24 the assumption that analgesic duration is a measure of analgesic action at the MOR might not be valid, as drug clearance is an important component of analgesic duration. Owing to its lipophilicity, spinal fentanyl has a low spinal cord bioavailability and is cleared by crossing the dura mater, where it is sequestered in epidural fat from where it returns to the systemic circulation via epidural veins.25 All of these stages are subject to between-subject pharmacokinetic and

Fig 1 Onset of pain relief following spinal analgesia and the effect of MOR A118G and hospital. VAPS assessed at baseline (the average of the three uterine contractions immediately before spinal analgesia) and during the first five successive uterine contractions after spinal analgesia. Data analysed using RM ANOVA (mixed linear models approach). (A) A118G: AA (blue) vs AG/GG (green); (B) Hospital: Miami (orange) vs Jerusalem (pink). All ‘within group’ analyses (AA, AG/GG, Jerusalem and Miami) revealed a progressive reduction of pain over successive uterine contractions after analgesia (P<0.001). Neither A118G nor hospital had a significant effect on time-course. The only time points at which there was a significant ‘between group’ difference for analgesia onset was for AA vs AG/GG at the third uterine contraction (P=0.050). Number of subjects per comparison group: Miami 80; Jerusalem 45; AA 91; AG/GG 34.
possibly pharmacogenetic factors that could affect the clearance of spinal fentanyl, unrelated to the affinity of opioid for spinal MORs.

Multifactorial nature of labour pain: multiple maternal–fetal and obstetric management factors affect the severity of labour pain, including parity,26 stage of labour,17 progress in labour,28 oxytocin use,29 induction of labour,30 time of day or night,23 and most importantly, the relative size of the pelvis31 and fetus.32

Exclusion of outliers: of the two subjects with known genotypes that were excluded because of analgesic failure, one was homozygous (GG). While narrow inclusion criteria improve the signal-to-noise ratio for central tendency, they can miss the real message in pharmacogenetic studies; the outliers. It is predominantly in these patients that the clinical challenges (variable analgesic response)8 and medical complications (apnoea)13 occur. Statistical analysis of the few GG subjects in this study was not possible owing to the small group sizes; however, visual inspection of the VAPS against time to analgesia request graph (Supplementary Fig. S3) suggested that they required analgesia earlier and at a lower VAPS.

Inadequate power to identify pharmacogenetic differences:
there are unique considerations when performing sample size calculations for gene association studies. Belfer and colleagues34 demonstrated that the relative risk of a SNP affecting phenotype was the single most important factor in determining sample size for allele-based association studies, followed in order by the prevalence of the phenotype and then the frequency of the SNP variant in the population, with the number of candidate genes tested trailing far behind in statistical importance. There was a relatively high allelic frequency of A118G in our population (14.8%). The prevalence of inadequate management of acute pain is ~20%.34 Based on their sample size reference curves, the sample size for assessing a single candidate allele under these circumstances would be ~50–100 subjects, on the condition that there was a 2.5-fold effect on the phenotype. The required sample size would rise to 200–300 subjects if there was only a 2-fold effect, and would reach 650–1000 subjects if there was only a 1.5-fold effect. Most studies have not demonstrated more than a 1.5-fold difference in clinical effect for the G118-SNP, none have enrolled 650–1000 patients, and all are probably underpowered. Larger studies in genetically stratified populations and gene–gene interaction studies13 35 might shed more light on the clinical implications of the MOR A118G SNP. Population based multi-array studies are likely to replace studies of candidate gene SNP.36

While it is likely that genetic variability may yet be shown to have a clinically relevant impact in analgesic response in general, this is likely to be limited for spinal opioids in labour analgesia, which depends on both spinal cord drug bioavailability and multiple maternal–fetal and obstetric management factors.

The marked effect of ethnically distinct hospital populations

All groups had similar onset of analgesia and pruritus after spinal fentanyl, but the duration of both was markedly shorter in the hospital population in Jerusalem compared with Miami. Ethnicity and hospital location were co-linear variables. As all the Hispanic and Black subjects were in Miami, and all the Jewish and Arab subjects were in Jerusalem, it is not possible to assess from these data whether the differences are attributable to ethnicity or to some other cause associated with local hospital population or practice.

There are several factors that reduce the likelihood that local hospital practice was the cause for the observed ethnic differences. Care was taken to use the same spinal needle and follow identical study protocols in both hospitals, and the same investigator E.M.D. directly supervised subject enrolment, spinal fentanyl administration and data...
collection in both locations. Peak drug effects and time to peak drug effects were identical in both locations, both for analgesia and for pruritus. There was no difference between the two hospitals in rates of labour induction or augmentation; furthermore oxytocin use (at least in Jerusalem) did not apparently affect the time until analgesic request. The observed inter-hospital differences in analgesic duration are not attributable to the increased analgesic requirement of more advanced labour, as cervical dilatation at enrolment was actually slightly higher (0.8 cm) in Miami.

Similarly, observed inter-hospital differences in analgesic duration are not attributable to the higher Caesarean delivery rate that was observed in Miami later in the study, after analgesic supplementation. The most common cause for these unscheduled Caesarean deliveries was poor progress and non-reassuring fetal heart rate, typically associated with relative cephalopelvic disproportion and impacted labour, factors that are strongly associated with more severe labour pain in early labour and an earlier (rather than a later) request for analgesia. Finally, although baseline pulse...
Fig 4 Onset and offset of pruritus: effect of MOR A118G and hospital. Pruritus over time assessed in the period from spinal analgesia until request for additional analgesia. Pruritus assessed in the upper plots (A, C, and E) by VAS (0–100 mm), mean (SD). Pruritus assessed in the lower plots (B, D, and F) by the percentage of subjects in each group that had VAS > 20 mm. Comparing pruritus over time for: (A and B) A118G SNP genotype: AA (blue) vs AG/GG (green); (C and D) Ethnicity: Blacks (blue), Hispanics (green) and Jew/Arab (light blue); (E and F) Medical centre: Miami (orange) vs Jerusalem (pink). (A, C, and E) Time curves for VAS assessed by RM-ANOVA; between-group effects reported on right-hand side of graphs. Significant differences at individual time points marked with asterisk and P-value. (A, D, and F) Time curves for % patients with pruritus > VAS 20 assessed by GEE (see Methods). Between-group effects reported on right-hand side of graphs. The number of subjects per comparison group: Miami 80; Jerusalem 45; AA 91; AG/GG 34.
Duration of analgesia and pruritus following intrathecal fentanyl

Table 3  Subject characteristics and obstetric baseline factors: 118A

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Ethnicity</th>
<th>Hospital</th>
<th>n</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>AA/AA</td>
<td>Jew/Arab</td>
<td>Miami</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>25.0 (4.2)</td>
<td>25.6 (3.7)</td>
<td>25.7 (3.1)</td>
<td>0.247†</td>
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<tr>
<td>80.2 (16.6)</td>
<td>78.8 (12.0)</td>
<td>80.3 (11.4)</td>
<td>0.387†</td>
<td></td>
</tr>
<tr>
<td>152.6 (6.9)</td>
<td>160.0 (7.4)</td>
<td>152.7 (7.1)</td>
<td>0.278†</td>
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</tr>
<tr>
<td>35.9 (1.5)</td>
<td>39.5 (1.9)</td>
<td>35.9 (1.5)</td>
<td>0.527†</td>
<td></td>
</tr>
<tr>
<td>3.2 (1.2)</td>
<td>3.2 (1.2)</td>
<td>2.7 (1.0)</td>
<td>0.740†</td>
<td></td>
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</tbody>
</table>

Analgesia and pruritus

Pruritus is a well-recognized side-effect that characterizes spinal opioid analgesia. We demonstrated identical time courses for the onset and offset of both pruritus and analgesia. Similarly, we demonstrated identical effects of independent variables (genomic group and ethnic/hospital population) on the onset and offset of pruritus and analgesia. Our confidence in the aforementioned between-group effects on fentanyl-induced analgesia is strengthened by identical between-group effects on fentanyl-induced pruritus.

The simultaneous onset of spinal analgesia and supraspinal pruritus has puzzled previous investigators. Analgesia and pruritus following spinal fentanyl have been demonstrated to exhibit identical dose-response relationships and are both antagonized by MOR antagonists. Our data contrast with the findings of two recent spinal morphine studies. Liu and colleagues administered spinal morphine to mice and demonstrated that analgesia and pruritus have different dose–response curves and a markedly different time course of action, with prolonged analgesic effect but pruritus of short duration. Gehling and colleagues observed similar findings in non-pregnant patients undergoing orthopaedic surgery. Liu and colleagues also demonstrated that morphine-induced analgesia and pruritus were mediated via different MOR isoforms. The lack of difference in offset time of analgesia and pruritus in our study might have been due in part to the use of spinal fentanyl, with its shorter duration of analgesic effect.

Summary

Following spinal fentanyl administration, we observed that ethnically distinct hospital population groups exerted a marked effect on the duration of both analgesia and pruritus, while we observed no significant effect for 118A>G (AA vs AG/GG). It is likely that the duration of labour analgesia is dependent on both spinal cord drug bioavailability and, especially, on multiple maternal–fetal and obstetric management factors.
**Supplementary material** is available at *British Journal of Anaesthesia* online.

**Authors' contributions**

Study conceived and designed by Y.G., E.M.D., Y.C., and D.J.B.; data collected by T.T.S., D.J.B., and E.M.D., genotyping performed by Y.C. Generalized linear model for RM of binary data performed by Dena H. Jaffe PhD, School of Public Health, Hadassah Hebrew University Medical Center, Jerusalem. All other statistical analysis performed by K.A. The manuscript was drafted by Y.G. and E.M.D. and revised critically for intellectual content by D.J.B., Y.C., T.T.S., and K.A. All authors approved the final version.

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**Declaration of interest**

The authors are not supported by, nor maintain any financial interest in, any commercial activity associated with the topic of this article.

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**References**


**Table 4** Obstetric outcome variables: MOR A118G, ethnic groups and hospital. Data expressed as mean (sd), or as counts (%) where appropriate. Data analysed as follows where indicated: *exact* for binary data as some tables have expected values <5; †one-way ANOVA. There was a marked difference in Caesarean delivery rate between hospital populations (which also drove the difference between ethnic populations); these all occurred after the request for additional analgesia; subjects who had Caesarean delivery or delivered before the request for additional analgesia were excluded from analysis (n=3).
Duration of analgesia and pruritus following intrathecal fentanyl


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