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
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. Two studies recorded upon enrolment in the study: age, height, weight, ethnic origin of both parents of the parturient, 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) at 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, Beerse, 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′-CGGTCTCCTGGGTCACACTTTCACCATTAGATGC-3′ and the reverse primer 5′-AGCCTGGAGTATAGGTGTCGTC-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 (so) 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%²⁴ 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 were excluded from final analysis. 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% we calculated a need to enrol 124 subjects.

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

<table>
<thead>
<tr>
<th></th>
<th>Total (n=125)</th>
<th>AA (n=91)</th>
<th>AG (n=31)</th>
<th>GG (n=3)</th>
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<tbody>
<tr>
<td>Ethnicity</td>
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</tr>
<tr>
<td>Jew/Arab</td>
<td>45 (36%)</td>
<td>31 (69%)</td>
<td>12 (27%)</td>
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<tr>
<td>Black</td>
<td>17 (14%)</td>
<td>17 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>60 (48%)</td>
<td>39 (65%)</td>
<td>19 (32%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (3%)</td>
<td>3 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Miami</td>
<td>80 (64%)</td>
<td>59 (74%)</td>
<td>19 (24%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Jerusalem</td>
<td>45 (36%)</td>
<td>32 (71%)</td>
<td>12 (27%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
(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 VAPS. 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 VAPS over the first five uterine contractions after spinal analgesia (Fig. 1). However, there was no significant difference detected between groups. There was also a predictable within-subjects time relationship for the increase in pain over the elapsed time from spinal analgesia until analgesic request (Fig. 2). 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 analgesic request. Within each ethnic group there was a significant difference between hospitals.

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 VAPS 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 VAPS (34 mm) (Supplementary Fig. S3); however these few subjects cannot be analysed statistically.

### Table 2

<table>
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<th>Genotype</th>
<th>Ethnicity</th>
<th>Hospital site</th>
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<td>AA (n=91)</td>
<td>Jew/Arab (n=45)</td>
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<tr>
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<td>Hispanic (n=60)</td>
<td>Miami (n=80)</td>
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<td></td>
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<td>Jerusalem (n=45)</td>
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<table>
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<tr>
<th>Time to request for analgesia (min)</th>
<th>VAPS at request for analgesia (0–100)</th>
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</thead>
<tbody>
<tr>
<td>Hispanic Jew/Arab Miami (n=45)</td>
<td>110.1 (41.5) 108.3 (48.8) 0.836 0.386</td>
</tr>
<tr>
<td>Hispanic Jew/Arab Jerusalem (n=45)</td>
<td>123.4 (46.2) 110.0 (12.3) 0.001 0.001</td>
</tr>
<tr>
<td>Black Jew/Arab Miami (n=17)</td>
<td>87.3 (32.1) 123.4 (46.2) 0.470 0.470</td>
</tr>
<tr>
<td>Black Jew/Arab Jerusalem (n=17)</td>
<td>68.7 (23.1) 68.7 (23.1) 0.360 0.360</td>
</tr>
<tr>
<td>Other (n=3)</td>
<td>54.9 (20.5) 54.9 (20.5) 0.650 0.650</td>
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### Table 3

<table>
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<th>Ethnicity</th>
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<td>Miami (n=80)</td>
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$P<0.05$; $P<0.001$
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 (T_{max}) 15 min. The onset and offset of pruritus exactly paralleled the time-course of analgesia as described above. The maximum pruritus VAS and T_{max} 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 enrolled 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 colleagues\(^\text{21}\) 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,\(^\text{18 21 24}\) 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.\(^\text{25}\) All of these stages are subject to between-subject pharmacokinetic and
Offset of pain relief following spinal analgesia and the effect of MOR A118G and hospital. The offset of spinal analgesia as reflected in VAPS measured at 15 min intervals until the request for analgesia. The VAPS at request of analgesia is not represented. Data analysed using RM ANOVA. (A) A118G: AA (blue) vs AG/GG (green); (a) Hospital: Miami (orange) vs Jerusalem (pink). All ‘within group’ analyses (AA, AG/GG, Jerusalem and Miami) revealed a progressive increase in pain over time after analgesia (P<0.001). There was a significant effect of hospital (Miami vs Jerusalem, P<0.001) but not of A118G (AA vs AG/GG, P=0.36) on the time-course of analgesia offset. The data for Jerusalem were truncated because no subject reached 150 min without requesting analgesia. Number of subjects per comparison group: Miami 80; Jerusalem 45; AA 91; AG/GG 34.

Fig 2 Offset of pain relief following spinal analgesia and the effect of MOR A118G and hospital. The offset of spinal analgesia as reflected in VAPS measured at 15 min intervals until the request for analgesia. The VAPS at request of analgesia is not represented. Data analysed using RM ANOVA. (A) A118G: AA (blue) vs AG/GG (green); (a) Hospital: Miami (orange) vs Jerusalem (pink). All ‘within group’ analyses (AA, AG/GG, Jerusalem and Miami) revealed a progressive increase in pain over time after analgesia (P<0.001). There was a significant effect of hospital (Miami vs Jerusalem, P<0.001) but not of A118G (AA vs AG/GG, P=0.36) on the time-course of analgesia offset. The data for Jerusalem were truncated because no subject reached 150 min without requesting analgesia. 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, stage of labour, progress in labour, oxytocin use, induction of labour, time of day or night, and most importantly, the relative size of the pelvis and fetus.

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) and medical complications (apnoea) 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 colleagues 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%. 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 studies 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.

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.
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 3 Time to analgesia request and the effect of MOR A118G, ethnicity and hospital: survival analysis. Kaplan–Meyer survival graphs for time until request for supplemental analgesia after spinal analgesia. Data compared between groups by Cox regression analysis. (a) A118G: survival curves for AA and AG were almost identical (P=1.0); GG is drawn in dashed lines for illustration only, as the small number of GG subjects prevents statistical analysis. (a) Ethnicity: there was no difference between Blacks and Hispanics (P=0.705), or between Ashkenazi and Sephardi Jews (P=0.472). However, there was a significant difference between the ethnic groups in Miami and Jerusalem: Blacks vs Ashkenazi Jews, P=0.047; Blacks vs Sephardi Jews, P=0.006; Hispanics vs Ashkenazi Jews, P=0.005; Hispanics vs Sephardi Jews, P<0.001. Arabs were drawn for illustration only, as the small number of subjects prevents statistical analysis. (c) There was a significant difference between Miami and Jerusalem (P<0.001). (D) Hospital/genotype interaction: within each hospital subgroup, A118G had no effect on time to analgesic request. There was a statistically significant difference between AA (Miami) vs AA (Jerusalem) (P<0.001) and between AG/GG (Miami) vs AG/GG (Jerusalem) (P=0.016). However, as all Hispanic and Black subjects were in Miami, and as all Jews and Arabs were in Jerusalem, it is not possible to assess whether the differences are attributable to ethnicity or hospital. A118G had no clinically relevant effect on time to analgesia request. Number of subjects per comparison group: Miami 80; Jerusalem 45; AA 91; AG/GG 34.
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. (B, 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.
Following spinal fentanyl administration, we observed a marked effect on the duration of both analgesia and pruritus, with no significant effect for 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.

Pruritus is a well-recognized side-effect that characterizes spinal 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 both pruritus and analgesia. The simultaneous onset of spinal analgesia and supraspinal pruritus following spinal fentanyl has been demonstrated in non-pregnant patients undergoing orthopaedic surgery. Liu and colleagues demonstrated that morphine-induced analgesia and pruritus have different dose–response curves, and are both antagonized by MOR antagonists. Our data demonstrated that morphine-induced analgesia and pruritus following spinal fentanyl administration are both antagonized by MOR antagonists and are both antagonized by MOR antagonists. Our data demonstrated that morphine-induced analgesia and pruritus have different dose–response curves and are both antagonized by MOR antagonists. Our data demonstrated that morphine-induced analgesia and pruritus have different dose–response curves and are both antagonized by MOR antagonists. Our data demonstrated that morphine-induced analgesia and pruritus have different dose–response curves and are both antagonized by MOR antagonists.

In contrast, the fact that ethnic groups exhibited similar analgesic responses only to other ethnic groups in the hospital supports the likelihood that these differences were caused by some underestimated or unidentified factor. There was no impact of baseline haemodynamic variables on the time to analgesic request. Ethnicity has been identified as a factor in the perception of pain and could have contributed to the differences observed in the analgesic response to fentanyl. Following spinal fentanyl administration, we observed a marked effect on the duration of both analgesia and pruritus on both spinal cord drug bioavailability and, especially, on multiple maternal–fetal and obstetric management factors.
Supplementary material

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. or Y.G. 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

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