A prospective cohort study comparing early opioid requirement between Chinese from Hong Kong and Caucasian Australians after major abdominal surgery

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Editor’s key points

- Individual patient response to opioids may be affected by a range of factors.
- Ethnic differences reflect both genetic and cultural heritage.
- This study examines opioid response and pain in two ethnically different groups after surgery.
- A reduction in opioid use, with more pain and pruritus, was found in Chinese patients.
- Further work is needed to explore ethnic variability in opioid response.

Background. The relationship between ethnicity and early opioid consumption is not well understood. Our prospective cohort study tested whether Chinese patients in Hong Kong require less opioid after major abdominal surgery compared with Caucasian patients in Australia.

Methods. Matched cohorts of patients from Hong Kong (n=68) and Australia (n=68) were recruited. Patient attitudes and expectations to pain management documented. After operation, all patients received i.v. morphine using a patient-controlled analgesia device. Postoperative opioid consumption, pain intensity, and incidence of opioid-related side-effects were recorded.

Results. The average (so) opioid requirement (i.v. morphine equivalent) at 72 h after surgery was significantly less among Chinese patients [86.8 (62.6) mg (95% CI 71.8, 101.8)] compared with Caucasian patients [130.6 (71.9) mg, (P, 0.0005) (95% CI 113.4, 147.8)]. Numeric rating scale pain score (0–10) was, however, higher in Chinese patients compared with Caucasian Australians, 5.3 (2.7) vs 4.4 (2.3) (P=0.029). The incidence of pruritus among Chinese patients was significantly higher than Caucasians at 24–48 h (P=0.001) and 48–72 h (P=0.001). Chinese patients also reported a strong preference for others to manage their pain, and their nurse carers were more likely to expect severe pain after surgery.

Conclusions. Chinese patients in Hong Kong required less opioid and experienced greater pain intensity and pruritus than Caucasian patients. Clinicians should consider differences in the side-effect profile of morphine and patient expectations related to pain control when planning postoperative analgesia for patients of Chinese ethnicity.

Keywords: acute pain; analgesics, opioid; general surgery

Accepted for publication: 7 May 2012

Race relates to groups of people with common ancestry and distinctive physical characteristics, whereas ethnicity also includes cultural influence.1 Ethnicity may affect pain experience. It is commonly believed that Asian populations experience lower pain score and require less opioid after surgery.2–4 In this regard, Asian patients appear more stoical, passive, and are more fearful of opioids leading to under-reporting of severe postoperative pain.5–9 Carer education may also be inadequate, and hence patient report of pain may be ignored.9 On the other hand, higher morphine clearance has been described among Asians.9 10 Furthermore, a substantial proportion of Asian populations possess genetic variations such that opioid receptors may show resistance to the therapeutic effects and side-effects experienced with μ-agonist drugs.11

Previous studies show either no difference in postoperative use of opioids5 12 or lesser opioid requirement among Asian populations compared with Caucasians.2 3 However, these studies involved single multiracial populations, and may have underestimated the effects of ethnicity. We therefore conducted a study to compare factors that may affect opioid requirement among the dominant ethnic populations in two countries. We aimed to simultaneously measure postoperative opioid use, severity of pain, and
incidence of opioid-related side-effects after major abdominal surgery between Caucasians in Melbourne and Chinese patients in Hong Kong. We hypothesized that Chinese patients require less opioid after major abdominal surgery than Caucasians.

Methods

Recruitment

The study evaluated two groups of adult patients (age 18–80 yr) simultaneously presenting for elective open abdominal surgery at the Alfred Hospital in Melbourne, Australia, and Prince of Wales Hospital in Hong Kong, Republic of China, between September 2007 and June 2010. This study was approved at both institutions by respective ethics committees (Alfred Hospital #178/07 and Prince of Wales Hospital CRE 2008.285). All patients provided written informed consent. Australian patients were eligible for the study if they and both their parents had strong Caucasian physical features and had spent most of their life in Australia. Similarly, patients in Hong Kong had to possess strong Chinese physical features and have lived in Hong Kong for most of their life. All patients agreed to receive patient-controlled analgesia (PCA) with morphine for at least 3 days after surgery and demonstrate adequate understanding on the principles involving the use of PCA.

We excluded patients if they were allergic to morphine, non-steroidal anti-inflammatory drugs, paracetamol or tramadol, or had pain necessitating >2 weeks of opioid therapy before surgery. Patients were also excluded if they had persistent pain for >3 months in the 6 months before surgery, or had pre-existing hepatic or renal impairment, or preferred regional techniques for postoperative analgesia.

Preoperative survey and PCA education

Before surgery, patients were surveyed, in their native language, regarding their attitudes about and understanding of postoperative pain and the use of opioids. Nurses who cared for the patients on the ward were also surveyed, in their native language, about the same themes. Patients and nurse carers were then provided with standardized educational materials, including an explanation on the nature of pain measurements using an 11-point numeric rating scale (NRS, where 0=no pain and 10=worst possible pain), the role of PCA, and a discussion about the importance of adequate analgesia to enable deep breathing and coughing after surgery. Patients and nurse carers were reassured that addiction was unlikely if the morphine PCA was used for pain control after major operation. At the end of the session, researchers reviewed the goals of education with the patients and nurses to ensure that the key messages were understood.

Intraoperative analgesia

All patients received general anaesthesia. There was no restriction on anaesthetic administration with the exception that ketamine was avoided. Volatile-based anaesthesia including the use of nitrous oxide was allowed. Intraoperative analgesia was, however, restricted to i.v. morphine, titrated to achieve adequate analgesia according to the clinical judgement of the attending anaesthetists. All patients received i.v. parecoxib 40 mg during surgery. No local anaesthetics were used.

Postoperative analgesia

After surgery, all patients were transferred to the postanaesthetic care unit where they received further i.v. boluses of morphine if NRS pain score was ≥4 or upon patient request. Patients were then provided with a PCA machine for 72 h. The PCA was programmed to deliver i.v. morphine boluses of 1 mg with a lockout interval of 5 min. Patients who rated their pain score >7 or who were affected by side-effects related to morphine administration were reviewed by independent pain physicians not involved in the study. Rescue analgesia included i.v. paracetamol 1 g, and if deemed ineffective within 2 h, i.v. tramadol 100 mg was administered. All patients continued to receive PCA and the data were included in the analysis. We converted tramadol dosage into equipotent i.v. morphine equivalent (i.v. tramadol dose divided by 15) and added this to the total opioid requirement.

Measurements

The primary endpoint was opioid requirement within the first 72 h after the start of surgery, measured as i.v. morphine equivalent dosage. NRS pain score was measured at rest, and with coughing, upon waking from surgery, and at 24, 48, and 72 h after surgery. We surveyed the patients and nurses to determine their views on a range of statements. These included ‘I am frightened of addiction if I use too much opioid after my operation’, ‘I expect severe pain after my surgery’, ‘I believe pain is part of my illness’, ‘I prefer others to manage my pain’. Patients were asked to record whether they strongly disagreed, disagreed a little, had neutral feelings, agreed a little, or strongly agreed. We also enquired as to patient expectation in relation to analgesic regimen: ‘the pain relief I expect after my surgery is: none/weak analgesia/strong analgesics/strong and weak analgesics’. Surveyed statements among nurse carers were similar to that of the patients: ‘I prefer to give my patient less opioid because of addiction’, ‘My patient should expect to have severe pain after surgery’, ‘The analgesia I expect that my patient will need: no analgesics/weak analgesics/strong analgesics/combinations of weak and strong analgesics’, ‘My patient should control their own analgesia therapy’. We also recorded the level of sedation (1, awake and alert; 2, asleep but easily aroused; 3, asleep and difficult to rouse; 4, unrousable), presence of pruritus, and presence of nausea or vomiting upon waking from surgery, and at 0–24, 24–48, and 48–72 h after surgery. At 72 h after surgery, patients were asked to rate their degree of satisfaction with analgesia (1, very satisfied; 2, somewhat satisfied; 3, unsatisfied; 4, unsure).
Pharmacogenomics
We tested patients from both groups for \( \mu \)-1 opioid receptor (OPRM1) polymorphism to evaluate the effect of a single-nucleotide polymorphism (SNP), A118G (rs1799971), on patient response to morphine analgesia.\(^\text{11}\) Genomic deoxyribonucleic (DNA) was extracted from blood samples using QIAampDNA mini kit 250 (Qiagen, Valencia, CA, USA). Genotyping was performed using Taqman SNP assays (Applied Biosystem, Foster City, CA, USA).

Statistical analysis
Power analysis was calculated for the primary endpoint. A total sample size of 136 patients was required to detect a 20% difference in opioid requirement between the two ethnic groups assuming 5% type I error and 20% type II error. Data were expressed as means (\( \pm \)SD), median (inter-quartile range), or numbers, as appropriate. Continuous data were analysed using two-tailed Student's \( t \)-test. Categorical and ordinal data were analysed using Fisher's exact test and the Mann–Whitney test, respectively. Pain scores were compared between Caucasians in Australia and Chinese from Hong Kong using a generalized linear model for repeated measures. The confounding effect of nitrous oxide on opioid requirement was examined using a multivariable regression with an interaction term examining ethnicity and age. Further subgroup analysis on the effect of nitrous oxide was done by two-tailed Student's \( t \)-test.

Results
There were 68 Chinese patients from Hong Kong and 68 Caucasian Australian patients included in the study. Table 1 shows the characteristics of the patients. Age, gender, duration of surgery, length of incision, and number of patients requiring postoperative paracetamol did not differ between the groups. Types of surgery in each population were also similar. Chinese patients had significantly lower BMI (\( P<0.0005 \)) and lower educational level (\( P<0.0005 \)). However, there were more patients in Hong Kong receiving nitrous oxide than Australia (\( P<0.001 \)). There were more patients in Australia (\( n=13 \)) needing additional doses of tramadol compared with the Chinese patients in Hong Kong (\( n=6 \)), but the number of patients was small and this was not statistically significant (\( P=0.10 \)).

Cumulative opioid requirement, expressed as morphine equivalent dose, at 72 h after the start of surgery was significantly lower in Chinese compared with Australians, 86.8 (62.6) vs 130.6 (71.9) mg (\( P<0.0005 \)) (Fig. 1). The difference remains significant when patients requiring rescue analgesics with paracetamol, tramadol, or both were excluded from the analysis, Chinese patients: 79.4 (50.2) mg vs Caucasian Australians: 120.1 (66.5) mg (\( P<0.0005 \)). When opioid requirement was adjusted for BMI, the difference between ethnic groups became smaller, but this was still significantly lower in Chinese patients, 3.8 (3.2) mg kg\(^{-1} \) m\(^{-2} \), compared with Caucasian Australians, 4.9 (2.9) mg kg\(^{-1} \) m\(^{-2} \) (\( P<0.029 \)). Similarly, Chinese patients required less opioid after discharge from the operating theatre, 77.7 (78) mg compared with Caucasian Australians, 111.4 (69.7) mg (\( P=0.009 \)). The severity of pain and opioid-related side-effects are summarized in Table 2. Despite lower opioid consumption...
among Chinese patients, it is interesting to note that pain scores with coughing were significantly higher in Chinese compared with Caucasian Australians ($P=0.029$). Chinese patients were significantly less sedated at 24–48 h ($P=0.012$) and 48–72 h ($P=0.047$), and reported a higher incidence of pruritus. After excluding patients requiring tramadol as rescue analgesia, the incidence of pruritus among Chinese was still higher than that in Caucasians after 24 h; 0–24 h: $P=0.05$; 24–48 h: $P=0.005$; 48–72 h: $P=0.03$. The correlation between itch and amount of opioid was low ($r = -0.05$) ($P=0.61$). The incidence of nausea and vomiting did not differ between the two ethnic groups. Chinese patients expressed lower satisfaction with pain management compared with Caucasian Australians ($P=0.009$).

Multivariable regression analysis showed that only ethnicity ($P<0.001$) and age ($P<0.0001$) affected opioid requirement. The use of nitrous oxide ($P=0.39$), gender ($P=0.98$), current smoking ($P=0.99$), and heavy alcohol intake (>3 standard drinks/day, $P=0.50$), however, did not influence opioid requirement.

Attitudes and knowledge towards postoperative pain management for patients and nurse carers are listed in Tables 3 and 4, respectively. Chinese patients were more likely to expect severe pain after surgery and preferred others to manage their pain ($P<0.0005$). On the other hand, Australian nurses were less likely to expect a patient to control their own pain after surgery.

Genotyping was completed in all patients. The minor allele frequency of the $\mu$-1 opioid receptor (OPRM1) variant gene was 12% among Chinese patients and 33% in the Australian cohort. Chinese patients who were homozygous for the minor allele required more opioid, 103.7 (59.6) mg, compared with the wild-type (AA), 69.3 (47.6) mg. However, the sample size remains small, and the difference was not significant ($P=0.05$). A larger proportion of Australian patients were homozygous carriers for the minor allele (GG, 33%), but the opioid requirement in these patients, 126.9 (70.7) mg, was similar to those of the wild-type (AA), 126.4 (57.9) mg ($P=0.98$).

**Discussion**

In this prospective cohort study, postoperative opioid requirement was significantly different between the dominant ethnic populations in two separate countries undergoing abdominal surgery.

### Table 2 Pain intensity score (0–10), sedation, presence of pruritus, nausea or vomiting, and satisfaction rating after major abdominal surgery among Chinese patients from Hong Kong and Caucasian patients in Australia. Values are mean (so), median (inter-quartile range), or numbers. *Repeated-measures analysis of variance

<table>
<thead>
<tr>
<th>Presence of pruritus</th>
<th>Chinese from Hong Kong</th>
<th>Caucasian Australian</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 h</td>
<td>17 (8)</td>
<td>8</td>
<td>0.05</td>
</tr>
<tr>
<td>24–48 h</td>
<td>16 (3)</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>48–72 h</td>
<td>14 (2)</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of nausea, vomiting, or both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>32 (31)</td>
<td>31</td>
<td>0.94</td>
</tr>
<tr>
<td>24–48 h</td>
<td>27 (20)</td>
<td>20</td>
<td>0.31</td>
</tr>
<tr>
<td>48–72 h</td>
<td>20 (15)</td>
<td>15</td>
<td>0.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Satisfaction rating</th>
<th>Chinese from Hong Kong</th>
<th>Caucasian Australian</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (1–2)</td>
<td>1 (1–1)</td>
<td>1</td>
<td>0.009</td>
</tr>
</tbody>
</table>

### Table 3 Survey of attitudes and knowledge among Chinese patients from Hong Kong and Caucasian patients in Australia. Values are expressed as median (inter-quartile range). *1, strongly disagree; 2, disagree a little; 3, neutral; 4, agree a little; 5, strongly agree. †1, no pain relief; 2, weak analgesics; 3, only strong analgesics; 4, strong and weak analgesic

<table>
<thead>
<tr>
<th>Statements provided to patients</th>
<th>Chinese in Hong Kong</th>
<th>Caucasians in Australia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am frightened of addiction if I use too much opioid after my operation*</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.37</td>
</tr>
<tr>
<td>I expect severe pain after my surgery*</td>
<td>5 (3.5–5)</td>
<td>3 (2–4)</td>
<td>0.0005</td>
</tr>
<tr>
<td>I believe pain is part of my illness*</td>
<td>3 (1–4)</td>
<td>3 (1.3–4)</td>
<td>0.62</td>
</tr>
<tr>
<td>The pain relief I expect after my surgery is...†</td>
<td>3 (2–4)</td>
<td>4 (3–4)</td>
<td>0.045</td>
</tr>
<tr>
<td>I prefer others to manage my pain</td>
<td>5 (4–5)</td>
<td>3 (2–4)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
Educational attainment was significantly higher among Caucasian patients in Australia. Lower level of education is a risk factor for the development of chronic pain after acute trauma and may be related to poorer understanding of PCA technique. It is plausible that Chinese patients in Hong Kong had more difficulty in conceptualizing the use of PCA and this may have contributed to a decrease in self-administration of opioid.

Chinese patients in Hong Kong were less satisfied with their pain management compared with Caucasian patients in Australia. This is most likely due to a higher incidence of pruritus leading to a reduction in postoperative opioid consumption. Satisfaction with pain management is related to the desire for analgesia, overall pain intensity, and functional capacity. The relative importance of these elements may differ between ethnicities and is dependent on the type of pain. Our study raises the question that susceptibility to opioid-related side-effects may partly explain some of these ethnicity-related differences in pain measurement.

In a retrospective study, nitrous oxide provided better postoperative pain relief and was associated with earlier cessation of PCA. Chronic post-surgical pain is also less common after nitrous oxide-based anaesthesia. In our study, more patients in Hong Kong received nitrous oxide, and this could theoretically contribute to lower opioid requirement. Nevertheless, we could not identify any association between nitrous oxide exposure under general anaesthesia and opioid consumption after our multivariable analysis.

Previous studies have identified gender differences in opioid consumption during the early postoperative period with conflicting findings. In a Caucasian-dominated multi-racial population, women experienced more pain and required more morphine to achieve a similar degree of analgesia. In another large cohort, Asian females consumed significantly less opioid. Similarly, smoking and heavy alcohol intake have been shown to increase postoperative opioid consumption. We were, however, unable to demonstrate significant influence of gender, smoking, and alcohol on opioid requirement in our study.

Higher morphine clearance has been described among Asian patients. Although we did not study the pharmacokinetics of morphine, the increased incidence of pruritus among Chinese patients would suggest that an increase in morphine metabolism is unlikely to greatly influence opioid consumption in this study.

We have also demonstrated that Chinese patients in Hong Kong were more likely to expect severe pain after major surgery. They were also more comfortable in having others to control their analgesic management. Our data confirmed greater passivity among Chinese patients, and a reluctance to use the PCA more aggressively to achieve functional goals. Other studies have suggested that fear of addiction is a potential explanation for the lower postoperative opioid consumption in Asians. Our data challenge this theory as both ethnic groups did not believe that they were at risk of

### Table 4 Survey of attitudes and knowledge among nurses in Hong Kong and Australia.

<table>
<thead>
<tr>
<th>Statements provided to nursing carers</th>
<th>Chinese in Hong Kong</th>
<th>Caucasians in Australia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I prefer to give my patient less opioid because of addiction*</td>
<td>1 (1–3)</td>
<td>2 (1–2)</td>
<td>0.01</td>
</tr>
<tr>
<td>My patient should expect to have severe pain after surgery*</td>
<td>3 (3–4)</td>
<td>2 (1–4)</td>
<td>0.0005</td>
</tr>
<tr>
<td>The analgesia I expect that my patient will need...</td>
<td>4 (4–5)</td>
<td>4 (4–5)</td>
<td>0.71</td>
</tr>
<tr>
<td>My patient should control their own analgesia therapy*</td>
<td>5 (4–5)</td>
<td>4 (3–4.8)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

major abdominal surgery. We demonstrated that opioid requirement was lower among Chinese from Hong Kong than that of Caucasians in Australia. The decrease in opioid consumption in Chinese patients was largely unaffected by the use of rescue analgesics, when dosage was adjusted for BMI or after exclusion of intraoperative opioid use. Associated with the lower opioid consumption, Chinese patients reported higher pain scores.

We also noted that Chinese patients reported a higher incidence of pruritus. The presence of pruritus is an unpleasant feeling and may explain the avoidance of opioid use, despite greater postoperative pain among the Chinese patients. Opioid-induced pruritus is thought to be related to peripheral histamine release. Nevertheless, a spinal mechanism has been proposed. Opioid receptor OPRM1 polymorphism has also been linked to pruritus with patients carrying the minor allele of A118G SNP showing less pruritus after intra-thecal morphine. Although a greater proportion of Caucasian patients in Australia were found to carry the minor allele (GG) in our study, we were unable to detect a correlation between this SNP and pruritus in our small number of patients.

Sedation was less common among Chinese patients than that of Caucasians in Australia, and this is likely to be related to lower opioid consumption. Interestingly, previous studies comparing Chinese and Caucasian patients in single multi-racial populations suggested that Chinese patients have greater susceptibility to sedation, nausea, and vomiting after opioid administration. The desire to avoid sedation in Chinese patients or for Caucasian patients to seek more analgesia and accept greater levels of sedation may contribute to the difference in opioid requirement between the two ethnic groups.
opioid dependence. Ethnic minorities in multiracial populations are less likely to receive adequate opioid\textsuperscript{12, 27} or be offered PCA\textsuperscript{28} after surgery. While inadequate patient education has been highlighted as a detrimental factor to pain experience,\textsuperscript{1} we standardized patient education and training before the study and nursing staff understood the importance of using strong analgesics to treat postoperative pain.

Our sample size was not designed to detect a genetic difference in opioid requirement, and may have explained the exceptionally high proportion (33\%) of Caucasian patients who received morphine alone during the first 3 days after surgery. Although patients with $\mu$-opioid receptor (OPRM1) homozygous GG variants are associated with opioid resistance, there was no difference in opioid requirement between Caucasian patients carrying AA or GG SNPs. We believe that genetic polymorphism alone cannot explain the higher opioid requirement in Caucasian patients.

There are limitations in this study. Many patients required rescue analgesia, and this may have obscured the difference in opioid requirement between the two ethnic populations. Nevertheless, we were able to demonstrate a significant difference in opioid consumption in the subgroup of patients who received morphine alone during the first 3 days after surgery.

In conclusion, we have shown that early opioid consumption after major abdominal surgery was significantly less among Chinese patients from Hong Kong compared with Caucasian patients in Australia. Implications for future clinical practice are that clinicians should be mindful of greater potential for morphine-induced pruritus in Chinese patients. Clinicians should be aware of the difference in cultural attitudes that may influence the patterns of opioid use and pain experience between Chinese and Caucasian patients.

Acknowledgements
The authors thank Professor Paul Myles, the Alfred Hospital, for his assistance with statistical analysis, and Professor Bruce Jacobs from Monash University, Melbourne, for his insights into cultural behaviours and attitudes of Asians.

Declaration of interest
None declared.

Funding
This study was supported by the Pain Research Fund at the Alfred Hospital, the Australian and New Zealand College of Anaesthetists Project Grant (11/012), and General Research Fund of the Research Grant Council, Hong Kong.

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