Gender and pain – is it an issue?

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More and more differences in perioperative responses between the sexes in a wide range of areas are being reported in the literature. Many factors including age and co-morbidity are instinctively considered by the anaesthesiologist when considering peri-operative morbidity. The gender of the patient is emerging as a possible indicator of morbidity which needs to be addressed as more data on differences in cardiac physiology and anatomy, gender differences in pain perception, different outcomes following trauma haemorrhage and brain injury are being reported in the anaesthetic literature. Two of the areas that are particularly pertinent to the anaesthesiologist are gender differences in pain perception, and gender differences in the peri-operative presentation and management of ischaemic heart disease.

Gender differences in pain perception

The reporting on gender pain differences is often difficult to interpret because the terms “sex” and “gender” are used interchangeably. According to the Institute of Medicine definition, sex is the “classification of living things, generally as male or female according to their reproductive organs and function” and gender is “a person’s self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual’s gender presentation”. The relative importance of biological, psychological and social influences on pain reporting and experiences in males and females is a complex field, making objective analysis difficult.

Epidemiology of gender differences in pain

Females report more frequent bouts of pain, more severe pain and longer lasting pain than males with similar diseases. Females have a higher prevalence of pain of musculoskeletal and visceral origin, as well as auto-immune disease related pain.

Because females are more likely to visit a doctor than males, pain reporting can be overestimated. The differences in pain perception change as the age of the patient increases and the disease process progresses. To negate these influences many pain related studies are performed on rodents.

Animal studies

Baseline differences

Female rodents have a lower pain threshold in experimental models of hot thermal, chemical, inflammatory and mechanical noiception. In a post-incisional pain model similar to the inflammatory neuropathic pain seen in humans after surgery, no sex differences in pain perception between female and male rodents was shown. Female rodents responded differently to males to non-drug induced anti-nociception. Stress-induced anti-nociception (SIA) is greater in male rodents, whereas in exercise-induced analgesia (EIA) both male and female rats showed decreased sensitivity to morphine-induced analgesia, probably due to increased endogenous β-endorphin levels.

Drug-induced anti-nociception

Opioids

In studies published since 2000, male rodents had a greater response to opioids in 70% of cases. However, 19% of studies showed an equal response between male and female rodents, and 11% indicated greater anti-nociception in males. These discrepancies are difficult to explain, but one plausible explanation can be found in the fact that opioid analgesia is produced by μ, κ or δ receptor stimulation. Male rodents appear to show a stronger anti-nociceptive effect to μ-agonists, whereas females react better to κ-agonists. The biological basis for this μ/κ dichotomy between males and females seems to be supported by genetic studies. Mogil et al. discovered that the gene for melanocortin-1 receptor (MC1) mediated κ-opioid agonist anti-

Table 1: Sex prevalence of clinical pain syndromes or diseases

<table>
<thead>
<tr>
<th>Bodily area</th>
<th>Prevalence</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female &gt; male</td>
<td>Female &lt; male</td>
</tr>
<tr>
<td>Head</td>
<td>Chronic tension</td>
<td>Cluster</td>
</tr>
<tr>
<td></td>
<td>Migraine with aura</td>
<td>Migraine without aura</td>
</tr>
<tr>
<td></td>
<td>Postdural puncture</td>
<td>Posttraumatic</td>
</tr>
<tr>
<td></td>
<td>Cervicogenic</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Temporal arteritis</td>
<td>Paratrigeminal syndrome</td>
</tr>
<tr>
<td></td>
<td>Occipital neuralgia</td>
<td>Trigeminal post herpetic neuralgia</td>
</tr>
<tr>
<td></td>
<td>Odontalgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burning mouth</td>
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<tr>
<td></td>
<td>Temporomandibular disorder</td>
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</tr>
<tr>
<td></td>
<td>Trigeminal neuralgia</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>Carpal tunnel syndrome</td>
<td>Brachial plexus neuropathy</td>
</tr>
<tr>
<td>Arms</td>
<td>Raynaud’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRPS type 1</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>Scleroderma</td>
<td>Meralgia paraesthetic</td>
</tr>
</tbody>
</table>
|                   | Chronic venous insufficiency | Got 
|                   | Peroneal muscular atrophy | Intermittent claudication |
|                   | Piniformis syndrome | |
|                   | Raynaud’s disease | |
|                   | CRPS type 1 | |
| Viscera           | Chronic constipation | Duodenal ulcer |
| Bowel             | Irritable bowel syndrome | |
| Oesophagus        | Proctalgia fugax | |
| Pancreas          | Oesophagitis | |
| Gall bladder      | Postcholecystectomy pain | |
| Auto-immune       | Lupus erythematosus | Reiter’s syndrome |
|                   | Multiple sclerosis | |
|                   | Rheumatoid arthritis | |
| Psychogenic       | Fibromyalgia | |

CRPS = Complex regional pain syndrome
Table modified from Wall and Melzack’s textbook of Pain, 5th Ed.
Positron emission tomography (PET) has been used to investigate differences, objective measures of pain have been investigated. Psychosocial effects on pain perception as a reason for gender catastrophise more than men, and this can account for sex differences in pain tolerance, with sex differences becoming insignificant after 40 years of age.18 Advancing age is associated with increased pain threshold and tolerance, with sex differences becoming insignificant after 40 years of age.18

**Socio-cultural influences on pain perception**

Pain tolerance is highly variable and influenced to a large degree by gender ‘norms’. Males who identify strongly with the male role tolerate more pain than females, while this difference disappears in males who do not have this belief.19 Gender roles also influence pain threshold differences. Males reported less pain and higher thresholds when tested by a female examiner. This effect was more pronounced when the examiner was attractive. Females, on the other hand, report more pain and lower thresholds with attractive male examiners.20

Maladapted pain coping strategies, such as catastrophising, are associated with poorer tolerance of clinical pain and higher sensitivity to experimental pain.21 Women are reported to catastrophise more than men, and this can account for sex differences in pain perception. In an attempt to eliminate psychosocial effects on pain perception as a reason for gender differences, objective measures of pain have been investigated. Positron emission tomography (PET) has been used to investigate regional brain activation after a painful thermal stimulus in females and males. Mismatch results have been reported.22 Functional magnetic resonance imaging showed no sex-based differences in brain activation after matched pain intensity stimuli.23

**Non-drug-induced analgesia**

In women, stress produces increased pain thresholds in males. In humans, stress produces no increase in pain threshold in men but does in women. Exercise induced analgesia shows similar findings with females showing the greatest increase in pain threshold and tolerance, after isometric exercise or running on a treadmill.24

**Drug-induced analgesia**

**μ-receptor agonists**

Analgesia to μ-receptor agonists

In an experimental electrical pain model, it was found that morphine is more potent in women than in men (lower C50 value), the onset/offset of morphine is slower in women than in men, and plasma concentrations of morphine and its metabolites M-6-G and M-3-G were identical in men and women.25 This explains why PCA morphine studies have indicated that women require more morphine in the first hours after surgery before analgesia sets in. This means that women require 20 – 30% larger morphine titration doses when compared with men.26 This 2 – 3 times slower onset of action of morphine is possibly due to slower passage of the drug across the blood-brain barrier. Interestingly, this disappears in elderly patients. This could possibly indicate a hormonal effect on the passage of morphine across the blood-brain barrier.

Some studies have shown an absence of sex differences to μ-agonists. The reason for these discrepancies is not simple to explain, but various factors could contribute to the absence of gender differences:

- Very low doses of opioids on the flat portion of the dose response curve would not show sex differences.27
- Differences in pain models used.
- Absence of reporting on drug plasma concentrations.
- Differences in specific end-points measured and opioids used (different μ-opioid agonists may activate different intracellular G-proteins.)28

**Side-effects related to μ-opioid receptor**

As a rule of thumb, women experience more side effects and of greater intensity following μ-opioid receptor agonists than men do.

i. Nausea and vomiting

In a retrospective study, 50% less nausea was observed in men than women, after short-term use of opioids (pethidine, morphine or fentanyl) after minor surgery.29 In a prospective study an even larger disparity was found with nausea occurring in 55% of women versus 3% in men following morphine administration.28

ii. Respiratory depression

There is compelling evidence of the existence of sex differences in opioid-induced respiratory depression. In a study by Dahan et al.30 qualitative and quantitative differences between sexes with greater respiratory depression in females was observed. This corresponds with the greater analgesic potency in women compared with men and probably shares a common underlying mechanism.

iii. Cardiovascular effects

After low-dose (0.08 mg/kg) intravenous (IV) morphine, cardiovascular responses between men and women showed significant differences. Men, but not women, developed hypertension at this dose, while lower heart rate values occurred in women. Of more importance, the cardiovascular response to ischaemic pain was attenuated in men only.28

iv. Subjective effects

Women experience subjective feelings such as a dry mouth, heavy feeling or “spaced out” feeling more than men. No difference in motor function between the sexes has been reported.31

**κ-opioid receptor agonists**

Gear et al.32 showed that nalbuphine, butorphenol and pentazocine (but NOT morphine) produced better and larger pain relief in women than in men following dental surgery. Two other studies failed to demonstrate this gender difference in experimental pain models (heat pain, pressure pain and ischaemic pain).12,28 None of the latter studies reported on plasma concentrations.
of the drug used, a relevant parameter as t1/2 elimination of pentazocine is greater in women than men.33

Sex differences in κ-opioid analgesia has been linked to the melanocortin-1 receptor gene.33 It has been shown that this gene modulates κ-opioid signalling in females only. Women, but NOT men, with two or more variant alleles of the MCM1 gene (all with red hair) show significantly greater analgesia from pentazocine than women without variants or only one variant. Women are associated with fair skin, freckles and red hair in humans. It is possible that MC1 receptors present in the brain are involved in modulation of nociception. Activation of these receptors by endogenous neuromodulators (dopamine) produces anti-opioid action in females only.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have been shown to influence pain tolerance in human studies, but have no effect on pain threshold. In an experimental pain model, ibuprofen produced an increase in pain tolerance in men, but not in women.33 Although there is a non-sexual inter-individual difference in response to NSAIDs, a lack of response to ibuprofen in female subjects in this study indicates that gender might explain some of these differences. There is no disparity in anti-inflammatory action of NSAIDs, only analgesic efficacy, between men and women. This is probably why this gender difference has not been reported in clinical studies.

In summary, although both animal and human studies report sex and gender differences in pain, the reasons for these differences remain elusive. Possible explanations include molecular and genetic mechanisms, while other factors include psychological, social, cultural and experimental bias. These differences may affect how we treat our patients peri-operatively. However, we need more studies to offer clarity on the matter.

Perioperative management of ischaemic heart disease in women

Introduction

In 43% of cases women do not demonstrate chest pain as a presenting symptom of angina.33 Women are 4-5 times more likely to have a false positive exercise test even with normal coronary angiography,36 and 60% of women investigated for chest pain have no stenotic lesions of their coronary arteries despite persistent chest pain.37 Actual ischaemia may thus be missed peri-operatively because of these atypical modes of presentation, which are probably caused by microvascular coronary involvement.

Pathophysiological differences

Hormonal effects

Cyclical hormonal changes (menstrual cycle / pregnancy / menopause) may account for difference in cardiovascular responses between men and women. Oestrogen has anti-atherosclerotic effects, reduces cellular hypertrophy and possesses anti-oxidant and anti-inflammatory properties.33 Oestrogen induces nitric oxide (NO) synthetase gene coding, resulting in vasodilatation and an age matched lower blood pressure in premenopausal women than men.35 Conversely, during menopause, the lack of cyclical oestrogen leads to progressive increases in the incidence of hypertension and pulse pressure. Menopause is also associated with decrease in HDL and an increase in LDL and triglycerides.

In the myocardium, oestrogen receptor-α and oestrogen receptor-β are upregulated by oestrogen.40,41 Oestrogen has been shown to decrease sympathetic activation. In post-menopausal women, females can develop acute left heart failure with emotional or physical stress in the absence of coronary artery disease (CAD) (Takotsuba Syndrome). These women have higher levels of circulating catecholamines.42

There is an increased incidence of diastolic dysfunction in women compared to men in later life. The causes are multifactorial, but a combination of hypertension, a stiffer aorta and higher total peripheral vascular resistance may explain the higher rate of diastolic failure.60 Oestrogens receptor-α and oestrogen receptor-β are upregulated by pressure overload.61 Oestrogen may be beneficial in preserving diastolic distensibility in post-menopausal women through effects on renin-angiotensin NO and Ca2+ metabolism in the myocardium.62

Coronary artery physiology in women

Women have smaller coronary arteries and less collateral myocardial circulation than men, leading to an increased incidence of ischaemia when myocardial work is increased. This is independent of body surface area.

Electrophysiology

Baseline heart rate is 4–5 beats/min higher in women than in men. Due to a higher baroreflex sensitivity women respond faster to changes in blood pressure, but with less heart rate response to these changes.43

The rate corrected QTc interval is prolonged in women and they are more likely to develop ventricular arrhythmias.44 Drugs which prolong the QTc interval are more likely to cause torsade de pointes in women who have a prolonged QTc interval at baseline. Women also develop more episodes of pathological tachycardia, and AV-nodal re-entrant tachycardias than men.

Preoperative risk stratification

Women not only differ in the pathophysiology and symptomatology of CAD, the accuracy of routine preoperative tests for cardiac risk stratification is also different.

Clinical signs and symptoms

Chest pain is not the typical presenting symptom of angina in women, but rather vague symptoms such as fatigue, dyspnoea and lack of energy.35 Older women present with acute coronary syndrome from an area of myocardial work is increased. This is independent of body surface area.

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based on studies in which either gender was not considered, or mixed groups were only used. However, differences in outcomes between men and women have been described after cardiac surgical interventions and high-risk non-cardiac vascular procedures.

Evidence suggests that different pathophysiology and clinical presentation of CAD in women warrants reconsideration of current risk stratification strategies geared to identify men at risk. The male anatomy and physiology is different to that of women: smaller heart size, narrower coronary arteries, increased risk. The female anatomy and physiology is different to that of men. Different renin-angiotensin-aldosterone systems and different sex-related differences in nociception systems and different response to drugs. These should all affect peri-operative outcome and management.

In future our perioperative management strategies will need to be tailored more specifically to the patient, also taking into consideration the patient’s gender. This will help in managing gender-related differences in pain and postoperative recovery.

References: