Postoperative pain, morphine consumption, and genetic polymorphism of IL-1β and IL-1 receptor antagonist

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Received 30 January 2006; received in revised form 15 May 2006; accepted 16 May 2006

Abstract

Interleukin-1 beta (IL-1β) and its endogenous IL-1 receptor antagonist (IL-1Ra) play an important role in inflammatory response and in pain modulation. It has recently been shown that polymorphism of the IL-1β and IL-1Ra genes may account for variation in the production of these cytokines. The present study examined the hypothesis that polymorphism of IL-1β and IL-1Ra genes is involved in pain sensitivity and morphine consumption in the immediate postoperative period. Genetic polymorphism was determined in 76 women undergoing transabdominal hysterectomy. The genotype of IL-1Ra was determined using PCR amplification of the variable number of tandem repeats (VNTR) of 86 base pair (bp) in intron 2, while for IL-1β the cytosine to thymine transition at codon −511 of the promoter was determined by PCR. Morphine consumption and pain scores were evaluated in the first postoperative 24 h. The study group was divided based on morphine consumption to three sub-groups: low morphine consumers (LMC) (<28 mg/24 h), medium morphine consumers (MMC) (28–38 mg/24 h), and high morphine consumers (HMC) (>38 mg/24 h). Patients consuming the least amount of morphine postoperatively showed significant lower pain scores. IL-1Ra genetic polymorphism of the MMC group was significantly different compared to the other two groups. No difference in IL-1β gene polymorphism was found among the three sub-groups. Since IL-1Ra polymorphism is known to affect the levels of both IL-1β and IL-1 cytokines associated with modulation of pain sensitivity and morphine analgesia, it is suggested that IL-1Ra genetic polymorphism may contribute to the variation in postoperative morphine consumption.

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Keywords: IL-1β and IL-1Ra gene polymorphism; Postoperative pain; Morphine consumption

Surgery-associated tissue injury sets off a cascade of related events, accompanied by elevated levels of proinflammatory cytokines, such as interleukin (IL)-1β and IL-6, both of which play an important role in postoperative pain. These cytokines can induce peripheral and central sensitization, leading to pain augmentation (hyperalgesia) [33]. IL-1β is involved in the mechanism of allodynia, and possibly in the development of postoperative neuropathic and chronic pain [4,26]. We have recently shown that effective postoperative pain management techniques were associated with attenuated production of proinflammatory cytokines and with lower pain experience [1,2].

Anti-inflammatory cytokines are also released at the time of inflammation, including IL-1 receptor antagonist (IL-1Ra), and can attenuate inflammatory hyperalgesia. It has been shown that formalin-induced hyperalgesia is significantly enhanced by spinal administration of IL-1 [33], and reduced by spinal administration of IL-1Ra [32].

Recent evidence suggests that the degree and severity of surgery-induced inflammation may be significantly influenced by genetic polymorphism [18]. Such polymorphism can be expressed as changes in the rate of gene transcription, the stability of the messenger RNA, or the quantity and activity of the ensuing protein. Genetic polymorphism of proinflammatory cytokines may contribute to the wide individual differences in IL-1β and IL-1Ra production observed in humans [6,7], and in this way may influence inflammatory response to surgery and postoperative pain. The genes for IL-1α, IL-1β, and IL-1Ra are all located on the long arm of chromosome 2. Two biallelic base change polymorphisms in the IL-1 gene have been reported: One is in the
promoter region at position −511; the other in exon 5 at position +3953 [27]. The polymorphic region within intron 2 of the IL-1Ra gene contains variable numbers of a tandem repeat of 86 base pairs (bp), and alleles 1–5 can be identified according to the size of the amplified DNA product [11].

Genetic polymorphism of IL-1β has been shown to influence its production by in vitro activated peripheral blood mononuclear cells [16,21]. Recently, it has been demonstrated that IL-1Ra genotype is the principal determinant of IL-1β bioactivity within the IL-1 gene cluster, regulating both constitutive and stimulated IL-1Ra and IL-1β release [28]. Allele 2 of the IL-1Ra gene (IL1RN*2) was consistently associated with higher IL-1Ra release, while allele 1 (IL1RN*1) homozygotes were found to release more IL-1β than carriers of at least one IL1RN*2 allele [28].

The present study sought to determine whether genetic polymorphism of IL-1β and IL-1Ra is associated with pain intensity and morphine consumption during the first 24 h of the postoperative period.

Seventy-six female patients (ASA physical status 1–2), 34–72 years old, who underwent transabdominal hysterectomy, were included in the study after we obtained an approval from the Hospital Human Studies Committee and an informed consent from the patients. On the preoperative visit, patients were equal sub-groups (n = 25, 25, and 26): low morphine consumers (LMC) included patients who used less than 28 mg of morphine per 24 h (mean = 20.7 ± 1.8 mg, n = 25), medium morphine consumers (MMC) used 28–38 mg/24 h of morphine and IL-1Ra and their frequencies in healthy individuals [10]. The alleles IL1RN*1, IL1RN*2, IL1RN*3, IL1RN*4, and IL1RN*5 represent four, two, five, three and six repeats of 86 bp tandem, with the size of 410, 240, 500, 325, and 595 bp, respectively.

The single base pair polymorphism at position −511 in the promoter region of the IL-1β gene was analyzed by the PCR-restriction fragment length polymorphism method. A 304-bp PCR fragment of the IL-1β promoter region was amplified using the following primers: 5′-TGGCATGTAACCTGCTTCCATC-3′ and 5′-GTGGAGGTCTTCCACCCTTT-3′. PCR conditions were as follows: a denaturing step of 95 °C for 10 min, then 36 cycles of 94 °C for 45 s, 54 °C for 50 s, 72 °C for 2 min, and final incubation at 72 °C for 5 min. The products were digested with 5 U of Avul (Promega, WI, USA) at 37 °C for 4 h and were run on an ethidium bromide-stained 2% agarose gel. This gave products that either remained intact (allele 2; IL-1B-511*2) or were cut into two fragments of 190 and 114 bp (allele 1; IL-1B-511*1).

Statistical analysis of the genotype distribution and allele frequency of the IL-1Ra and IL-1β genes polymorphism was carried out by χ²-tests and Pearson correlation coefficients. Differences in VAS scores and morphine consumption among the various genotypes and phenotypes for IL-1β, IL-1Ra and their combinations, were analyzed by ANOVA, and nonparametric Wilcoxon and Kruskal–Wallis tests. The results are expressed as mean ± S.D. The level of significance was determined as P < 0.05.

The average pain score (VAS) over 24 h treatment period was 1.85 ± 0.59 and 3.12 ± 0.81 at rest and during coughing, respectively. A strong linear correlation was observed between VAS scores at rest and during coughing (r = 0.803; P < 0.002). The mean accumulative dose of morphine consumption throughout the 24 h postoperative period was 53.25 ± 12.72 mg. No correlation was found between morphine consumption and VAS scores, either at rest or during coughing, corroborating earlier reports of lack of such relationship [8].

Morphine consumption in the first 24 postoperative hrs was rank ordered, and patients were then divided into three nearly equal sub-groups (n = 25, 25, and 26): low morphine consumers (LMC) included patients who used less than 28 mg of morphine per 24 h (mean = 20.7 ± 1.8 mg, n = 25), medium morphine consumers (MMC) used 28–38 mg/24 h of morphine.
Table 1

<table>
<thead>
<tr>
<th>Morphine consumption and VAS scores in the three subgroups</th>
<th>Whole group (n = 76)</th>
<th>LMC (n = 25)</th>
<th>MMC (n = 25)</th>
<th>HMC (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (mg/24 h)</td>
<td>33.1 ± 1.5</td>
<td>20.7 ± 1.0</td>
<td>32.0 ± 0.5</td>
<td>47.3 ± 1.9</td>
</tr>
<tr>
<td>VAS at rest</td>
<td>1.85 ± 0.59</td>
<td>1.62 ± 0.13</td>
<td>1.96 ± 0.11</td>
<td>1.87 ± 0.11</td>
</tr>
<tr>
<td>VAS during coughing</td>
<td>3.12 ± 0.82</td>
<td>2.83 ± 0.14</td>
<td>3.24 ± 0.15</td>
<td>3.23 ± 0.17</td>
</tr>
</tbody>
</table>

* LMC: low morphine consumers (<28 mg/24 h).
* MMC: medium morphine consumers (28–38 mg/24 h).
* HMC: high morphine consumers (>38 mg/24 h).

Table 2

<table>
<thead>
<tr>
<th>Allele</th>
<th>Genotype</th>
<th>n</th>
<th>1/1</th>
<th>1/2</th>
<th>2/2</th>
<th>1/3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IL1RN*1</td>
<td></td>
<td>0.283 (43)</td>
<td>0.065 (10)</td>
<td>0.065 (10)</td>
<td>0.065 (10)</td>
</tr>
<tr>
<td></td>
<td>IL1RN*2</td>
<td></td>
<td>0.535 (27)</td>
<td>0.1 (8)</td>
<td>0.13 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL1RN*3</td>
<td></td>
<td>0.13 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results are expressed as relative values, with absolute numbers in parenthesis.

* LMC: low morphine consumers (<28 mg/24 h).
* MMC: medium morphine consumers (28–38 mg/24 h).
* HMC: high morphine consumers (>38 mg/24 h).

Significantly different from LMC and HMC (P < 0.022).
it has recently been shown that IL-1/H9252 has an inhibitory role in pain sensitivity [31]. IL-1, as TNF or IL-18, indicates that the reduced pain sensitivity is impaired in signaling of other proinflammatory cytokines, such as the change in basal pain sensitivity was not observed in mice with a genetic blockade of IL-1 signaling displayed lower basal pain algesia produced by various inflammatory stimuli [5,19,20,30]. Small interfering RNA (siRNA) targeting antibodies, or with IL-1Ra, attenuate or block the hyperalgesia associated with intradermal injection of various inflammatory stimuli [2]. 

The present findings suggest that a genetic polymorphism in the IL-1Ra gene may affect morphine consumption in the postoperative period.

Acknowledgment

This study was funded entirely by the resources of the Department of Anesthesia, Rabin Medical Center, Golda-Hasharon Campus.

References


[34] L.R. Watkins, S.F. Maier, Beyond neurons: evidence that immune and cell contribute to pathological pain states, Physiol. Rev. 82 (2002) 981–1011.
