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## SCIENTIFIC ARTICLE

# Effect of intraoperative intravenous lidocaine on pain and plasma interleukin-6 in patients undergoing hysterectomy<sup>☆</sup>



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### KEYWORDS

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Postoperative pain;  
Hysterectomy;  
Interleukin-6

### Abstract

**Background and objectives:** Interleukin-6 is a predictor of trauma severity. The purpose of this study was to evaluate the effect of intravenous lidocaine on pain severity and plasma interleukin-6 after hysterectomy.

**Method:** A prospective, randomized, comparative, double-blind study with 40 patients, aged 18–60 years. G1 received lidocaine (2 mg kg<sup>-1</sup> h<sup>-1</sup>) or G2 received 0.9% saline solution during the operation. Anesthesia was induced with O<sub>2</sub>/isoflurane. Pain severity (T0: awake and 6, 12, 18 and 24 h), first analgesic request, and dose of morphine in 24 h were evaluated. Interleukin-6 was measured before starting surgery (T0), 5 h after the start (T5), and 24 h after the end of surgery (T24).

**Results:** There was no difference in pain severity between groups. There was a decrease in pain severity between T0 and other measurement times in G1. Time to first supplementation was greater in G2 (76.0 ± 104.4 min) than in G1 (26.7 ± 23.3 min). There was no difference in supplemental dose of morphine between G1 (23.5 ± 12.6 mg) and G2 (18.7 ± 11.3 mg). There were increased concentrations of IL-6 in both groups from T0 to T5 and T24. There was no difference in IL-6 dosage between groups. Lidocaine concentration was 856.5 ± 364.1 ng mL<sup>-1</sup> in T5 and 30.1 ± 14.2 ng mL<sup>-1</sup> in T24.

<sup>☆</sup> Study performed at the Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.

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**PALAVRAS-CHAVE**

Lidocaína;  
Via venosa;  
Dor pós-operatória;  
Histerectomia;  
Interleucina-6

**Conclusion:** Intravenous lidocaine ( $2 \text{ mg kg}^{-1} \text{ h}^{-1}$ ) did not reduce pain severity and plasma levels of IL-6 in patients undergoing abdominal hysterectomy.

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### Efeito da lidocaína venosa intraoperatória sobre dor e interleucina-6 plasmática em pacientes submetidas a histerectomia

**Resumo**

**Justificativa e objetivos:** A interleucina-6 (IL-6) é preditora de intensidade no trauma. O objetivo deste estudo foi avaliar o efeito da lidocaína por via venosa sobre a intensidade da dor e IL-6 após histerectomia.

**Método:** O estudo foi prospectivo, randomizado, comparativo e duplo-encoberto em 40 pacientes, entre 18 e 60 anos. Foi administrada lidocaína ( $2 \text{ mg.kg}^{-1}.\text{h}^{-1}$ ) no G1 ou solução salina a 0,9% no G2 durante a operação. A anestesia foi com O<sub>2</sub>/isoflurano. Foi avaliada a intensidade da dor (T0: despertar e seis, 12, 18 e 24 horas), a primeira solicitação de analgésico, a dose de morfina nas 24 horas. A IL-6 foi medida antes do início da operação (T0), após cinco horas do início (T5) e 24 horas após o término (T24).

**Resultados:** Não houve diferença na intensidade da dor entre os grupos. Ocorreu diminuição da intensidade da dor entre T0 e os outros momentos avaliados no G1. O tempo para primeira complementação foi maior no G2 ( $76,0 \pm 104,4 \text{ min}$ ) do que no G1 ( $26,7 \pm 23,3 \text{ min}$ ). Não houve diferença na dose de morfina complementar entre G1 ( $23,5 \pm 12,6 \text{ mg}$ ) e G2 ( $18,7 \pm 11,3 \text{ mg}$ ). Houve aumento das concentrações de IL-6 em ambos os grupos de T0 para T5 e T24. Não houve diferença na dosagem de IL-6 entre os grupos. A concentração de lidocaína foi  $856,5 \pm 364,1 \text{ ng.mL}^{-1}$  em T5 e  $30,1 \pm 14,2 \text{ ng.mL}^{-1}$  em T24.

**Conclusão:** A lidocaína ( $2 \text{ mg.kg}^{-1}.\text{h}^{-1}$ ) por via venosa não promoveu redução da intensidade da dor e dos níveis plasmáticos de IL-6 em pacientes submetidas a histerectomia abdominal.

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**Introduction**

Both the dose and duration of lidocaine infusion remain controversial. Moreover, its effectiveness has not yet been determined. Surgical trauma results in the release of cytokines that are responsible for local inflammatory responses and promote tissue healing.<sup>1</sup> Interleukin-6 (IL-6) is a cytokine that is early detected in response to injury and its increase is correlated with the degree of tissue damage.<sup>1,2</sup>

Some authors have reported that intravenous lidocaine promotes reduction of cytokines,<sup>3,4</sup> inhaled anesthetics<sup>5</sup> and opioids consumption,<sup>6,7</sup> and postoperative pain severity.<sup>3,6,7</sup> Furthermore, low doses of intravenous lidocaine (plasma concentrations less than  $5 \mu\text{g mL}^{-1}$ ) do not interfere with normal nerve conduction and are associated with a lower incidence of opioid-related adverse effects.<sup>3,6,8</sup>

Lidocaine has analgesic,<sup>6</sup> anti-hyperalgesic,<sup>6,9</sup> and anti-inflammatory effects.<sup>4,10</sup> Analgesia may persist even after plasma concentration reduction.<sup>10,11</sup>

The voltage-gated sodium channels are the classic targets of lidocaine.<sup>12</sup> The analgesic and anti-inflammatory action also occurs through calcium and potassium channels and receptors coupled to G protein.<sup>13,14</sup> The neuronal transmission blockade and reduced neurogenic response are

caused by the action on sodium and potassium channels.<sup>13,15</sup> Lidocaine metabolite, monoethylglycinexylidide (MEGX), may also exert analgesic effect.<sup>16</sup> Unlike MEGX, lidocaine reduces glycine uptake only at toxic concentrations. However, other studies reported no analgesic effect of lidocaine.<sup>17,18</sup>

Thus, the primary objective of this study was to evaluate the effect of intraoperative intravenous lidocaine on postoperative pain severity and plasma levels of IL-6 after abdominal hysterectomy.

**Methods**

After approval by the Research Ethics Committee of the Federal University of São Paulo and obtaining written informed consent, 40 patients, ASA 1 or 2, aged between 18 and 60 years, undergoing elective total hysterectomy by laparotomy through a Pfannenstiel incision were included.

Patients who experienced cardiac arrhythmia; cardiomyopathy; cardiac conduction abnormality; electrolyte disorders; acid-base imbalance; hypersensitivity to lidocaine; psychiatric, hepatic, respiratory or cancer disease; those receiving any type of painkiller in the week before

surgery or received blood products during the study period were excluded.

This was a prospective, double blind and randomized study. Patients were randomly allocated into two groups of equal size by lot to receive either lidocaine infusion (G1) or 0.9% saline infusion (G2/control). Randomization was performed using G1 and G2 registers, which were placed in sealed envelopes prior to study initiation and opened approximately 30 min prior to anesthesia by a physician who prepared the intravenous solution and identified it with the patient number, according to the envelope drawn. The solution was handed to another physician, blind to the prepared solutions' content, who was responsible for the anesthesia. The solution volume was equal. The responsible investigator remained blind to the chosen group until the end of the study.

G1 patients ( $n=20$ ) received  $2\text{ mg kg}^{-1}\text{ h}^{-1}$  of lidocaine and G2 patients ( $n=20$ ) received an equal volume of 0.9% saline, whose infusion was initiated at the time of induction of anesthesia and continued until the end of the operation.

Midazolam was administered at a dose of 15 mg orally 1 h before anesthesia. Patients were monitored with continuous electrocardiography and pulse oximetry and intermittent noninvasive blood pressure measurements every 5 min. Induction of anesthesia was performed with fentanyl ( $5\text{ }\mu\text{g kg}^{-1}$ ) and propofol ( $2\text{ mg kg}^{-1}$ ); neuromuscular blockade was achieved with atracurium ( $0.5\text{ mg kg}^{-1}$ ). Anesthesia was maintained with  $\text{O}_2$ /isoflurane at sufficient dose to maintain systolic blood pressure within the limit of 20% baseline value. Neuromuscular blockade was maintained with atracurium ( $0.2\text{ mg kg}^{-1}$ ) administered every 30 min. During surgery, additional doses of opioids or other analgesics were not used. There was no prophylaxis for postoperative nausea and vomiting.

After surgery, patients were monitored in the recovery room and later taken to the ward. Morphine (5 mg) was administered subcutaneously using a 23 G scalp, as necessary.

Blood samples were collected in ethylene diamine tetra acetate (EDTA) tubes immediately after contralateral upper limb venipuncture, before the operation (T0), 5 h after the start of surgery (T5), and 24 h after surgery (T24). Blood samples were centrifuged and plasma was separated and stored at  $-70^\circ\text{C}$  up to analysis. The levels of IL-6 were analyzed using the enzyme-linked immunoassay (ELISA). Lidocaine and its metabolite MEGX were analyzed using high performance liquid chromatography (HPLC) 5 h after the start of surgery and 24 h after surgery.

Pain severity was assessed at rest using a verbal numeric scale (VNS) from zero to 10 (where 0 = no pain and 10 = most severe pain possible). A verbal descriptive scale (VDS) was also used: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. The scores were recorded at the following times: T0 = immediately at awakening; T6 = 6 h after awakening; T12 = 12 h after awakening; T18 = 18 h after awakening; T24 = 24 h after awakening.

For postoperative analgesia, morphine (5 mg) was subcutaneously administered by a nurse, as needed. The first analgesic request, the supplemental dose of morphine necessary for the first 24 h, and the dose of isoflurane used intraoperatively were recorded; side effects were also recorded.

## Statistical analysis

Sample size calculation was performed with GraphPadInstat® program (GraphPad Software Inc., San Diego, CA, USA). For such, we considered the reduction of pain severity caused by lidocaine. Based on a pilot study conducted by the same research group, the standard deviation (SD) was estimated at 2.2. A difference of at least 3 in VNS (0–10) was considered clinically relevant. Because pain is subjective and individual, three levels of difference were considered a significant pattern of change or an improvement factor or a significant worsening. Confidence interval was 95%. Thus, a sample with a minimum of 20 patients per group was calculated. The following tests were used: Mann–Whitney test to compare age and body mass index (BMI); Student *t*-test to compare weight, height, duration of anesthesia, duration of surgery, time to first analgesic supplementation, total morphine consumption in 24 h, pain intensity, total isoflurane consumption, and IL-6 plasma levels. Data were expressed as mean  $\pm$  SD.

## Results

Fig. 1 shows the study flowchart.<sup>19</sup> The groups were similar regarding demographic data and duration of surgery and anesthesia (Table 1).

There was no difference between the two groups in the time points evaluated (Table 2). There was no statistically significant difference in IL-6 concentration between groups (Table 3).

The postoperative time to first morphine dose request for analgesia was higher in G2 ( $76 \pm 104.4$ ) than in G1 ( $26.7 \pm 23.3$ ) (Table 4). There was no difference between groups regarding supplementary morphine dose and volume of isoflurane (Table 4). Table 5 shows the concentrations of lidocaine and its metabolite, MEGX. Nausea occurred in seven patients in each group.

## Discussion

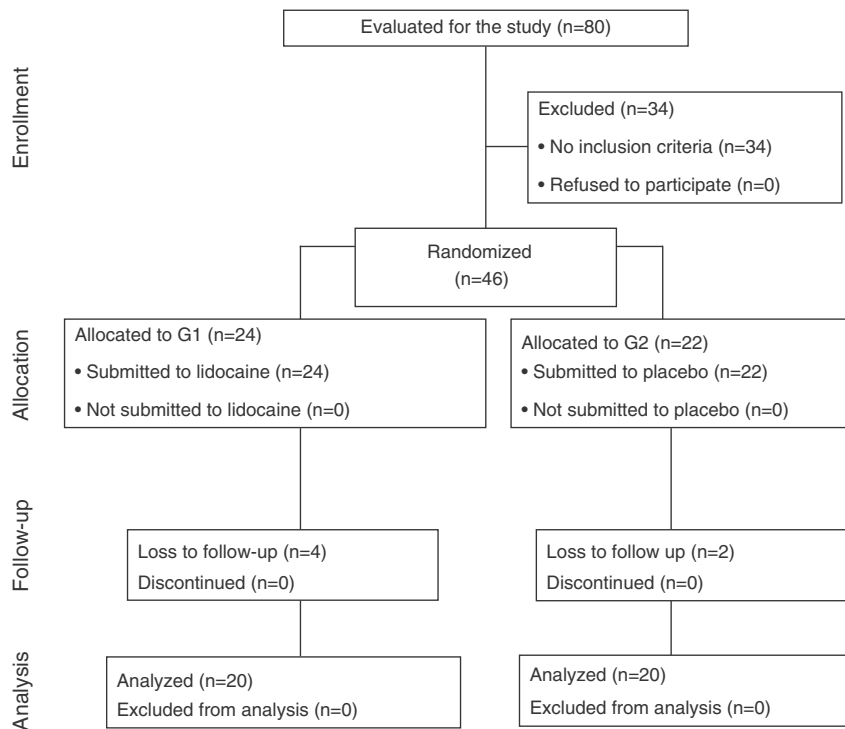
There was no analgesic effect with intravenous lidocaine infusion and also no reduction in plasma concentration of IL-6.

In this study, the open hysterectomy was chosen because it is associated with severe postoperative pain, with a great chance of changes in the neuronal processing of the spinal dorsal horn, which would allow us to compare the groups.<sup>20</sup>

Previous studies have used larger doses of lidocaine for intravenous infusion and some used initial bolus, which may explain the lack of analgesic effect in this study.<sup>3,5–7</sup>

In one study,<sup>3</sup> lidocaine ( $2\text{ mg kg}^{-1}$ ) was administered as a bolus and maintained with infusion of  $3\text{ mg kg}^{-1}\text{ h}^{-1}$ . In another study,<sup>6</sup> the analgesic and sparing effect of morphine was most evident on the third postoperative day, but this study was limited to 24 h.

It must be remembered that the dose and duration of lidocaine venous infusion, with the objective of obtaining postoperative analgesia, have not been well defined.<sup>21</sup> However, some studies have reported good results with low doses of lidocaine (plasma concentrations less than  $5\text{ }\mu\text{g mL}^{-1}$ ).<sup>6</sup>



**Figure 1** Flowchart based on Consort.<sup>19</sup>

**Table 1** Demographic data, operation and anesthesia times.

	G1	G2	<i>p</i>
Age (years)	44.1 ± 6.6	42.9 ± 5.7	0.646 <sup>a</sup>
Weight (kg)	72.2 ± 13.7	74.2 ± 12.6	0.379 <sup>b</sup>
Height (cm)	159.12 ± 6.5	158.0 ± 6.6	0.343 <sup>b</sup>
BMI (kg m <sup>-2</sup> )	28.5 ± 5.4	29.7 ± 5.3	0.133 <sup>a</sup>
Operation time (min)	102.6 ± 49.4	93.0 ± 48.2	0.122 <sup>b</sup>
Anesthesia time (min)	145.1 ± 51.8	124.0 ± 43.8	0.172 <sup>b</sup>

G1, lidocaine; G2, saline solution; BMI, body mass index.

<sup>a</sup> Mann-Whitney test.

<sup>b</sup> Student's *t*-test.

**Table 2** Pain intensity by numerical rating scale.

Times (h)	G1 (n = 20)		G2 (n = 20)		<i>p</i>
	Scores	IC 95%	Scores	CI 95%	
T0	3.2 ± 3.9	1.3–5	2.5 ± 3.7	0.7–4.2	0.602
T6	1.4 ± 1.8	0.5–2.3	1.8 ± 1.6	1–2.5	0.307
T12	0.8 ± 1.5	0–1.4	1.3 ± 1.8	0.4–2.1	0.307
T18	0.9 ± 1.5	0.1–1.5	1 ± 1	0.5–1.5	0.476
T24	1 ± 1.6	0.3–1.8	1.3 ± 1.6	0.5–2	0.602

G1, lidocaine; G2, saline solution; CI 95%, 95% confidence interval; T0, awakening; T6, T12, T18 and T24, 6, 12, 18 and 24h after awakening.

Because the measurement of plasma lidocaine was not part of the purpose of this study and served only as additional information, its analysis was made at the same dosage times of IL-6: before beginning surgery (T0), 5h after the

start of surgery (T5) and 24h after the end of anesthesia (T24). As the longest surgery time in G1 lasted up to 210 min, blood sample was not collected during the intraoperative infusion of lidocaine. Therefore, it was not possible

**Table 3** Plasma concentration of IL-6 (pg mL<sup>-1</sup>).

Times (h)	G1 (n = 20)	G2 (n = 20)	p
T0	0.95 ± 4.25	2.56 ± 7.55	0.602
T5	20.34 ± 17.83	19.44 ± 17.88	0.841
T24	24.95 ± 14.82	34.73 ± 15.62	0.056

G1, lidocaine; G2, saline solution; T0, before surgical incision; T5, 5 h after the incision; T24, 24 h after skin suture.

**Table 4** Volume of isoflurane used, time to first analgesic request, and additional analgesic dose of morphine over 24 h (mean ± SD).

	G1 (n = 20)	G2 (n = 20)	p
Time to first supplementation (min)	26.7 ± 23.3	76.0 ± 104.4	0.046
Additional dose of morphine in 24 h (mg)	23.5 ± 12.6	18.7 ± 11.3	0.217
Volume of isoflurane used (mL)	25.2 ± 8.9	26.5 ± 10.6	0.679

G1, lidocaine; G2, saline solution; Student's *t*-test.

to measure the peak concentration of lidocaine. At T5 and T24, the measurement of lidocaine averaged 0.86 µg mL<sup>-1</sup> and 0.55 µg mL<sup>-1</sup>, respectively. These results are well below concentrations considered effective, which range from 2 to 10 µg mL<sup>-1</sup>.<sup>22</sup> In this study, intravenous lidocaine did not reduce postoperative pain severity, similar to some studies,<sup>16–18</sup> probably because of the short infusion time and absence of initial bolus dose.

Although it has been reported that there would be a higher analgesic effect that would increase the infusion time, instead of lidocaine dose, the study of Koppert et al.,<sup>6</sup> using low dose infusion of lidocaine for up to 1 h after surgery, showed positive prolonged results for up to 72 h. In our study, lidocaine infusion was discontinued at the end of surgery, as in other studies.<sup>3,5,8,23–26</sup> Lidocaine dose was based on the study by Lauwick et al.<sup>5</sup> Indeed, lidocaine bolus was not used before infusion because in some studies there was a reduction in postoperative pain with only the infusion.<sup>23,27</sup>

In this study, patients who received lidocaine required their first analgesic supplementation earlier than the control group. One possible explanation for this result may be a great individual variability in pain thresholds and patients' response to analgesics. Because there was considerable discrepancy in the first analgesic request time among patients in G2, the group standard deviation was greater than the mean.

Interleukin-6 (IL-6) is an early marker of tissue damage and its excessive and prolonged increase is related to greater postoperative morbidity.<sup>2</sup> In our study, IL-6 was measured before the start of surgery (T0), 5 h from the start of surgery

(T5), and 24 h after the end of anesthesia (T24), according to the plasma peak described in the work by Hong et al.,<sup>28</sup> in which IL-6 is detected in 60 min with blood peak between 4 and 6 h and may persist for 10 days.

There was a statistically significant progressive increase in IL-6 dosage in each group. The highest value was at the last collection time (24 h after surgical suture). This fact contrasts with the works by Lin et al.<sup>1</sup> and Herroeder et al.,<sup>4</sup> with IL-6 peak between 4 and 6 h in the postoperative period, and Kuo et al.,<sup>3</sup> with IL-6 peak 10 and 12 h after surgery. There was an increasing trend in the last dose of IL-6 in G2 compared to G1, which shows a possible anti-inflammatory effect of lidocaine or its active metabolite, MEGX, even after the end of infusion and beyond the half-life of elimination. Probably, a statistically significant difference would be shown between groups if the sample size was increased.

Experimental studies have shown that MEGX, but not lidocaine, increased the glycinergic activity (inhibitory neurotransmission) through GlyT1 blockade (glycine transporter-1) in central nervous system in clinically relevant concentrations.<sup>16,29,30</sup> In our study, the mean concentration of MEGX reached was 0.55 µg mL<sup>-1</sup> 5 h after the start of surgery, similar to the level which leads to the *in vitro* inhibition of glycine transport, which was observed during the continuous infusion of lidocaine.<sup>29</sup>

Unlike some previous studies,<sup>6,7</sup> lidocaine showed no isoflurane and morphine-sparing effect in our study. Furthermore, there was no difference in total morphine consumption between groups. Similarly, some studies have reported analgesic effect with lidocaine.<sup>17,18</sup> It is possible that these findings are related to unique patterns of peripheral and central sensitization that vary with the different type and location of surgeries.<sup>23</sup>

The analgesic effects of lidocaine are more pronounced when it is infused intraoperatively<sup>6</sup> and may continue for days or weeks, that is, beyond infusion time and plasma half-life,<sup>11,31</sup> indicating its action on other targets, not only the voltage-gated sodium channels, and suggesting a hypersensitivity prevention of the central or peripheral nervous system, or both.<sup>7</sup> In abdominal surgery, lidocaine has

**Table 5** Plasma levels of lidocaine and monoethylglycinexylidide (MEGX) (ng mL<sup>-1</sup>) in G1.

Times (h)	Lidocaine	MEGX
T5	856.5 ± 364.1	545.6 ± 212.9
T24	30.1 ± 14.2	ND

G1, lidocaine; T5, 5 h after the incision; T24, 24 h after skin suture; ND, not detectable.



decreased the duration of paralytic ileus, postoperative pain severity, and opioid consumption.<sup>32–34</sup>

A clinically significant reduction in pain severity was observed in the awakening time in relation to other measured time with lidocaine, but not in G2, which may reflect the beneficial effect of lidocaine or analgesic effect of morphine.

No other differences were observed between groups at any assessment time. In this study, intravenous lidocaine infusion during surgery ( $2 \text{ mg kg}^{-1} \text{ h}^{-1}$ ) without initial bolus did not improve postoperative analgesia or reduce IL-6 plasma levels in patients undergoing open abdominal hysterectomy.

More studies are needed to confirm these results and evaluate the beneficial effects of lidocaine in patients undergoing other types of surgery. Moreover, the appropriate dose, the onset time, and the duration of lidocaine infusion required to reduce the postoperative pain remain to be determined.

## Conflicts of interest

The authors declare no conflicts of interest.

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