# Abstract

Objective: To evaluate intraperitoneal (IP) lidocaine administration and intravenous (IV) lidocaine infusion for postoperative pain control after cesarean section. Study design: prospective randomized, double-blind, placebo-controlled study. Patients and methods: Initially, 165 pregnant full-term females, indicated to be underwent elective cesarean delivery for various indications were randomized equally to either group C (control, IP and IV saline), group IP (intraperitoneal lidocaine administration), or group IV (intravenous lidocaine infusion). Five patients were excluded from each group for various reasons. The outcome measures were postoperative pain scoring, total pethidine consumption and the need for postoperative analgesia. Results: Significantly reduced visual analogue scale scores after 4h, total pethidine consumption in 24 hours, time of ambulation, onset of pain relief and the need for rescue analgesia in groups IV and IP compared with controls. Postoperative nausea and vomiting were less frequently noted in groups IP and IV than in group C, but this trend was not statistically significant. Conclusion: The IP lidocaine instillation and IV lidocaine infusion significantly reduced postoperative pain and opioid consumption in women underwent elective cesarean section, compared with control infusions.
Title: Efficacy of intraperitoneal versus intravenous lidocaine for postcesarean pain relief

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<th>Name</th>
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A short title: Lidocaine for postcesarean pain relief.

Key words: Cesarean; Pain; Lidocaine; Intraperitoneal; Intravenous.
Introduction

Cesarean section is the most common laparotomy performed for women worldwide, and their rates are progressively rising (1). Postcesarean pain remains a major morbidity and optimal pain management is a crucial challenge in which obstetricians and anesthesiologists should be implicated and get responsibility (2).

An ideal method for postcesarean pain relief should be cost-effective simple, safe for the mother, has high-quality pain relief with low incidence of side effects and complications. Also, it would not interfere with the maternal care of newborn or with the establishment of breast-feeding and use drugs minimally excreted into breast milk (3). Several studies have been performed to assess the effectiveness of different postpartum pain management protocols for cesarean section. These protocols may be insufficient and unsatisfactory in some patients. Therefore; a multimodal approach to pain management including the use of nonsteroidal anti-inflammatory drugs, opioids, and local anesthetics has been suggested (4).

Local anesthetics usage during surgery has fewer side effects in compare with opioids or neuro-axial methods. A variety of local anesthetic techniques have been investigated to find out their potential analgesic benefits. Local anesthetic installation can be performed at the wound site in the form of incisional or around the nerves as a spinal, epidural, paravertebral or transversus abdominis plane block (5). Preliminary reports suggested that intraperitoneal installation of local anesthetics, thereby blocking peritoneal afferents, may have a beneficial effect after gynecological laparoscopic surgery and cesarean sections (6, 7). Also, intravenous Lidocaine infusion can offer postoperative analgesia especially after abdominal surgery (8). Based upon these considerations this study was conducted to compare the effect of intraperitoneal lidocaine installation to that of intravenous lidocaine injection on postoperative pain and analgesic requirements, in women undergoing cesarean section.

Patients and methods

This prospective, double-blind, placebo-controlled, randomized clinical study was done in OB/GYN Department of Benha University Hospital, Alkalubia, Egypt from June 2013 to
December 2015. The study protocol was approved by the Local Ethics Committee and written informed consents were taken from Participants entering the study. Initially, the study included 165 women with Singleton pregnancy, more than or equal completed 37 gestational weeks, indicated to undergo elective cesarean delivery for various indications e.g., primigravida with breech presentation, macrosomia, intrauterine growth restriction and contracted pelvis, and willing to participate in the study. Gestational age was determined on the basis of the last menstrual period, confirmed by an ultrasound before 20 weeks of gestation and calculated in menstrual weeks. Exclusion criteria: extreme of age (below 18 or above 40 year), uncooperative patients, women under spinal anesthesia, previous abdominal scars, including previous cesarean or myomectomy, multiple gestation, BMI >35 kg/m², chorioamnionitis, hypersensitivity or contraindications to lidocaine, bronchial asthma, bleeding diathesis, pregnancy induced-hypertension, liver or kidney diseases, diabetes mellitus, and patients with psychological disturbance, or any form of chronic pain before or during pregnancy.

Patients were randomized according to a computer generated random numerical table into 3 equal groups each included 55 participants. Group C (placebo control group): saline was given both intraperitoneally and intravenously during caesarean section. Group IP (intraperitoneal instillation group): patients received 1.75 ml/kg of 0.2% lidocaine (3.5mg/kg) with parietal peritoneal closure with intravenous normal saline in a volume equivalent to that used in intravenous lidocaine group as placebo to ensure blinding. Group IV (intravenous injection group): Patients received 1.5mg/kg of intravenous 1% lidocaine as bolus dose at induction and 2mg/kg/hour as continuous infusion of intravenous lidocaine until one hour after surgery and 100 ml of saline intraperitoneally as placebo to ensure blinding.

The preparation and administration of the medication were carried out by a nurse who had not been involved in the management of the patient except for drug administration. Data collection sheets with corresponding codes were filled out preoperatively by the operating surgeon. These sheets were completed postoperatively by residents. Patients were evaluated for postoperative pain scoring, total pethidine consumption and the need for postoperative
analgesia. The time to bowel sounds, starting regular diet duration of hospital stay and any reported side effects were also noted. The allocation was revealed for both patient and surgeon at the end of the study.

**Cesarean section technique:**

Cesarean section was performed always by the first author, however; patients follow-up was confirmed by the 2 other obstetricians. Cesarean section was conducted under general anesthesia (General anesthesia is indicated if the patient refuses a regional approach, if there is any clinical contraindication to neuraxial blockade e.g., coagulopathy, or when time is of immense necessity e.g., acute severe fatal compromise. Lack of resources, manpower, and skill and to a lesser extent, materials to insert a regional anesthetic, are further reasons for general anesthesia). Anesthesia was carried out by the fourth author of this study. Skin was incised via the Pfannenstiel incision followed by blunt dissection of the subcutaneous tissues, sharp opening of the anterior rectus sheath, and the rectus muscles were separated using the no cutting procedure. Subsequently blunt technique was used to open and expand the parietal peritoneum, high above the bladder, bladder flap was created. A small median transverse lower uterine segment hysterotomy incision was made using a scalpel, expanded bluntly on both sides. After delivery of the baby and the placenta and without exteriorization, the hysterotomy incision was closed using continuous nonlocking double layer closure. However, visceral peritoneum was left open in all patients. After closing the uterine incision the accumulated blood in the pelvis and haematomas were carefully wiped out with surgical towels, leaving a more or less dry pelvis before the fluid was instilled. The abdomen was closed in layers. Parietal peritoneum was closed using continuous nonlocking sutures. However, the rectus muscles were left nonapproximated. Closure of the subcutaneous tissue was done with single stitches. Closure of the skin was performed with a subcuticular suture. No intraabdominal, subrectal, or subcutaneous drains were left.

**Postoperative Analgesia:** Patient received declofenac sodium 75ml IM during the immediate postoperative period and repeated every 12 hours for the first 24 hours, additional rescue analgesia in form of pethidine 50mg IM upon patient request.
Patients were monitored for side effects such as nausea, vomiting, drowsiness, and itching.

**Pain Scoring:** All pain scores were obtained at interval 4, 6, 12, and 24 hours after surgery. To assess pain on the first postoperative day, the visual analog scale (VAS) was used to assess the procedure-related pain. The VAS is often presented as a horizontal 100 mm long line with verbal anchors saying no pain at one end and unbearable pain at the other end. The patient was asked to mark the line at the distance corresponding to the intensity of present pain. The VAS rating of 0–4 mm was considered no pain; 5–44 mm, mild pain; 45 to 74 mm, moderate pain; and 75–100 mm, severe pain. The VAS was explained to the patients before the procedure. Patients completed the VAS without the help of any staff member. Patients could not do it or did not want to finish it were excluded from pain analysis.

**Side effects:** Pethidine-related side effects noted were dizziness, sleepiness, nausea, vomiting, sweating, constipation, dry mouth. The lidocaine-related side effects noted were blurred vision, hearing problems, dizziness, peripheral paraesthesia, itching uncontrolled muscle contraction, convulsions, headache, hypotension and bradycardia.

**Sample size calculation:** The sample size of 50 women in each group was calculated by statistical computer program with following parameters: Probability of type 1 error was 0.05, power was 0.8, number of groups was 3, large difference to be detected among means was 0.54, and expected background SD was 1. The drop-out incidence was expected to be 10% so, 55 cases were enrolled in each group.

**The statistical analysis:** The collected data were tabulated and statistically analyzed using The Statistical Package for Social Sciences (SPSS, Chicago, USA) software version 15.0 for Windows. Results were expressed as mean ± standard deviation (SD). Comparison between the mean values of different variables in the three groups was performed using ANOVA test while proportions were compared using the chi-square test. P value less or equal to 0.05 was considered significant.
Results:

Figure 1 represented the CONSORT diagram showing the flow of participants through each stage of a randomized trial. No statistical differences were noted among the three groups as regarding age, weight, parity, gestational age, anesthesia time and operation time Table 1. Significantly reduced visual analogue scale scores were observed in groups IP and IV compared with controls after 4h; however this difference was not noted after 6h, 12h, and 24h Table 2. There were significantly lower total pethidine consumption in 24 hours, time of ambulation, onset of pain relief and the need for rescue analgesia in groups IV and IP compared with controls. No significant differences were noted between the groups regards the time to bowel sounds, the time to starting a regular diet or the period of hospital stay, although values were lower in Group IV compared with the other two groups. Postoperative nausea and vomiting were less frequently noted in groups IP and IV than in group C, but this trend was not statistically significant Table 2.
Discussion

The current study reported that installation of lidocaine either intraperitoneal or intravenous during caesarian section significantly reduced postoperative pain scores and opioid consumption. The intraperitoneal installation of local anesthetics to decrease postoperative pain has been evaluated in a variety of surgical occasions. These studies have compared different types of local anesthetics and different timing of local anesthetic delivery in relation to surgery, for example, preprocedure, via continuous catheter infusion or at the end of surgery. Several studies reported that intraperitoneal lidocaine at the end of surgery was coupled with lower postoperative pain scores after laparoscopic cholecystectomy (400mg lidocaine) (9), minor laparoscopic gynecological procedures (10), and total abdominal hysterectomy (200mg lidocaine) (11). However, its use in postcesarean delivery pain was evaluated in one study reporting a decreased incidence and scores of postoperative pain following intraperitoneal instillation of 200mg of lidocaine at the end of cesarean delivery, in which the parietal peritoneum was, sutured (7). Among the several local anesthetics for postoperative pain relief currently in practice the instillation of local anesthetics intraperitoneally during caesarian section has been most promising and best adapted to our practice, because of its possible efficacy and the simplicity and ease of realization by obstetricians. However, it involves the risk of turning a localized infection into generalized peritonitis. Therefore, IV lidocaine could be used as part of a multimodal approach to the treatment of postoperative pain, particularly when IP lidocaine administration is not reasonable, as in cases of serious intra-abdominal inflammatory conditions. (12).

In agreement with the results of the present study, different studies reported that intravenous lidocaine infusion decreased the opioid consumption, improves postoperative pain scores and bowel function in patients undergoing laparoscopic and abdominal surgeries and improved the life-quality postoperatively without affecting the time to discharge from the post anesthesia care unit (13, 14). The analgesic effect of systemic lidocaine is biphasic. It has a peripheral suppression effect on acute chemically induced pain and central antihyperalgesic
The optimal method for intravenous lidocaine delivery is not yet established. Large bolus lidocaine infusions was associated with a direct analgesic and morphine-sparing effect, however continuous low-dose lidocaine infusions were effective only in postoperative pain reduction (16). Therefore, in the present study, we used both bolus and continuous lidocaine injection to achieve a lasting analgesic effect and favorable postoperative outcomes.

The current study agreed with other studies reported that lidocaine either intraperitoneal or intravenous during caesarian section significantly reduced postoperative opioid consumption (7, 8, 9, 10). Opioid consumption is not only a reflection of pain intensity, but is also intensely influenced by diverse psychological factors including anxiety level, mood and expectation of recovery (9).

The side effects in both lidocaine groups compared to placebo were minimal. This can be explained by the high safety profile and the minimal toxicity from commonly studied lidocaine doses that well documented by previous studies (12). Another explanation would be the lower morphine consumption among lidocaine patients, resulting into less drowsiness, nausea, vomiting, itching, and earlier mobility, as reported by the present study.

The following are some limitations of this study:

i) Obese pregnant women with body mass index of >35 and patients receiving regional anesthesia were not included in the study.

ii) The nature of postoperative pain and the VAS score that corresponded to each type of pain was not characterized.

Conclusion

Intravenous lidocaine injection is as effective as intraperitoneal instillation compared to placebo for reducing pain, pethidine consumption and early ambulation in women undergoing elective cesarean section. The main advantage of intravenous lidocaine injection is that this is an easily and universally applicable procedure compared to that of intraperitoneal instillation.

Acknowledgment
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**Declaration of interest**

The authors had no conflict of interest to declare regarding this article.

**Funding**

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**References**


Figure 1: The CONSORT diagram showing the flow of participants through each stage of a randomized trial

Assessed for eligibility (n = 200)

Excluded (n = 35)
- Not meeting inclusion criteria (n = 20)
- Refused to participate (n = 15)

Randomized (n = 165)

Allocated to (control, IP and IV saline) (n = 55)
- Received allocated intervention (n = 53)
- Did not receive allocated intervention (n = 2) (Postpartum hemorrhage)

Allocated to (intraperitoneal lidocaine) (n = 55)
- Received allocated intervention (n = 54)
- Did not receive allocated intervention (n = 1) (Cesarean hysterectomy)

Allocated to (intravenous lidocaine) (n = 55)
- Received allocated intervention (n = 52)
- Did not receive allocated intervention (n = 3) (Postpartum hemorrhage)

Follow up

Lost to follow up (n = 1) (Early discharge)
- Discontinued intervention (n = 2) (could not complete VAS)

Lost to follow up (n = 2) (Early discharge)
- Discontinued intervention (n = 2) (could not complete VAS)

Lost to follow up (n = 1) (Early discharge)
- Discontinued intervention (n = 1) (could not complete VAS)

Analysis

Analyzed (n = 50)
- Excluded from analysis (n = 5)

Analyzed (n = 50)
- Excluded from analysis (n = 5)

Analyzed (n = 50)
- Excluded from analysis (n = 5)
Table 1: Demographic features of the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=50)</th>
<th>Intraperitoneal group (n=50)</th>
<th>Intravenous group (n=50)</th>
<th>p value</th>
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<tr>
<td>Age (y)</td>
<td>27.82 ± 4.41</td>
<td>27.88 ± 4.53</td>
<td>27.62 ± 3.85</td>
<td>0.42</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>76.23 ± 4.84</td>
<td>77.47 ± 4.21</td>
<td>76.91 ± 4.11</td>
<td>0.805</td>
</tr>
<tr>
<td>Parity</td>
<td>1.77 ± 0.21</td>
<td>1.82 ± 0.28</td>
<td>1.79 ± 0.11</td>
<td>0.488</td>
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<tr>
<td>Gestational age (wk)</td>
<td>38.6 ± 1.41</td>
<td>38.8 ± 1.304</td>
<td>38.2 ± 2.074</td>
<td>0.9216</td>
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<tr>
<td>Anesthesia time, min</td>
<td>49.4 ± 4.615</td>
<td>46.8 ± 3.962</td>
<td>48.2 ± 5.805</td>
<td>0.7054</td>
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<tr>
<td>Operation time, min</td>
<td>44.4 ± 4.615</td>
<td>42.2 ± 3.768</td>
<td>43.2 ± 5.805</td>
<td>0.7731</td>
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</tbody>
</table>

Data expressed as mean ± SD (standard deviation); y: year; Kg: kilogram; wk: week; min: minute.
Table 2: Outcome measures of the studied groups

<table>
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<th>Group</th>
<th>Control group (n=50)</th>
<th>Intraperitoneal group (n=50)</th>
<th>Intravenous group (n=50)</th>
<th>p value</th>
</tr>
</thead>
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<td>VAS</td>
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<tr>
<td>4h</td>
<td>56.00 ± 11.67</td>
<td>37.83 ± 11.21</td>
<td>37.2 ± 11</td>
<td>&lt;0.001*</td>
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<tr>
<td>6h</td>
<td>58.33 ± 10.60</td>
<td>55.17 ± 16.10</td>
<td>54.80 ± 16.22</td>
<td>0.115</td>
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<tr>
<td>12h</td>
<td>51.33 ± 8.92</td>
<td>48.33 ± 9.60</td>
<td>47.62 ± 9.04</td>
<td>0.210</td>
</tr>
<tr>
<td>24h</td>
<td>32.33 ± 8.10</td>
<td>35.17 ± 8.92</td>
<td>34.3 ± 8.37</td>
<td>0.397</td>
</tr>
<tr>
<td>Total pethidine consumption in 24 hours (mg)</td>
<td>74.88 ± 18.0</td>
<td>33.50 ± 12.76</td>
<td>31.01 ± 10.80</td>
<td>0.001*</td>
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<tr>
<td>Time of ambulation (hours)</td>
<td>5.97 ± 1.37</td>
<td>3.93 ± 1.36</td>
<td>3.86 ± 1.32</td>
<td>0.001*</td>
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<tr>
<td>Onset of pain relief (minutes)</td>
<td>23.0 ± 5.9</td>
<td>16.4 ± 6.4</td>
<td>15.8 ± 6.2</td>
<td>0.001*</td>
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<td>Need for rescue analgesia</td>
<td>34 (68%)</td>
<td>10 (20%)</td>
<td>9 (18%)</td>
<td>&lt;0.001*</td>
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<td>Time to bowel sounds, days</td>
<td>1.0 ± 0.55</td>
<td>0.96 ± 0.42</td>
<td>0.91 ± 0.5</td>
<td>0.312</td>
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<td>Time to regular diet, days</td>
<td>1.19 ± 0.4</td>
<td>1.03 ± 0.51</td>
<td>0.9 ± 0.52</td>
<td>0.532</td>
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<tr>
<td>Time to hospital discharge, days</td>
<td>1.55 ± 0.65</td>
<td>1.45 ± 0.52</td>
<td>1.35 ± 0.522</td>
<td>0.654</td>
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<td>Side effects</td>
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<tr>
<td>- Pethidine related</td>
<td>20 (40%)</td>
<td>12 (24%)</td>
<td>11 (22%)</td>
<td>0.18</td>
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<tr>
<td>- Lidocaine related</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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Data presented as mean ± SD (standard deviation), or number (%); VAS: Visual analogue scale.