Adjuvant Perioperative Intravenous Lidocaine is Effective and Safe for Postoperative Pain Management and Rehabilitation in Gynecology Surgery: A Randomized, Single-Blind, Placebo-Controlled Trial

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Abstract
Background: There is scant data on the effectiveness and safety of adjuvant perioperative intravenous (IV) lidocaine in procuring postoperative analgesia and rehabilitation in gynecology surgery in low-resource settings.

Objectives: To evaluate the effects of IV lidocaine on postoperative pain and rehabilitation gynecology surgery.

Methods: We carried out a randomized single-blinded controlled trial from April to August 2017 (5 months) at the Yaoundé Gynaecology, Obstetrics and Pediatrics Hospital, Cameroon. The study population was made up of ASA 1 and 2, women admitted for elective gynecological surgery under general anesthesia divided into two groups of 17 patients: those to receive IV lidocaine and those to receive normal saline as placebo both intra-and postoperatively as an adjuvant to standard care. The variables studied included the additional doses of fentanyl, postoperative pain, side effects of lidocaine, time to first bowel sounds, the ease with which patients were mobilized and patient satisfaction.

Results: Compared to patients in the placebo group, those in the lidocaine group had fewer mean amounts of fentanyl reinjections \((P<0.0001)\), shorter recovery time \((P=0.0044)\), reported lesser pain in the immediate postoperative period \((P=0.012)\) till the 3rd postoperative hour \((P<0.001)\), had more early postoperative bowel sounds \((94.1\% \text{ vs. } 11.8\%)\), rehabilitated earlier \((P<0.001)\) and were more satisfied with pain management \((P=0.001)\). The lone observed side effect of IV lidocaine was tolerable bradycardia in six (35.3%) patients.

Conclusion: Adjuvant IV lidocaine can be effectively used in gynecological surgery, with the advantage of better postoperative analgesia, quicker rehabilitation and minimal side effects.

Keywords: Lidocaine, Intravenous, Postoperative, Pain, Rehabilitation, Gynecology

1. Background
Nowadays, a fundamental objective of surgery is early postoperative rehabilitation through the “Fast-tract” concept. To achieve this, reducing postoperative pain to the most minimal level is primordial because postoperative pain is associated with poor clinical outcomes, patient dissatisfaction, and long-term morbidities such as chronic post-surgical pain. Other physiological effects of postoperative pain include reduced intestinal motility, altered renal physiology, impaired immune and coagulation function, muscle weakness, sleep disruption, and psychological distress. Postoperative pain is a strong predictor of whether patients are satisfied with their perioperative care. Unfortunately, approximately...
88% of patients report moderate to severe acute pain after surgery. Current evidence supports the routine use of multimodal analgesia in the perioperative period to avoid over-reliance on opioids for pain control and to reduce opioid-related adverse events. To this effect, the often advocated multimodal analgesia regimen consists of non-opioid systemic analgesics like acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentin, ketamine, and local anesthetics administered by tissue infiltration, regional block, or local anesthetics administered via the intravenous (IV) route.

Lidocaine is an amide local anesthetic. Its mechanism of action is by blocking sodium channels in nerve impulse transmission. It also shows an inhibitory effect on neuropeptide chemical mediators, which play an important part in the genesis of pain. If this effect can be achieved in the entire organism through systemic (IV) administration, the inflammatory response to surgical stress can be inhibited. This could go a long way to protect the organism from this exaggerated response, which affects several organs and is responsible for high patient morbidity, such as postoperative ileus. Recent studies have suggested that repeated IV doses or continuous infusion of lidocaine could enable proper pain management and preserve postoperative gastrointestinal motility. Reduction in perioperative consumption of anesthetic drugs has also been observed with IV lidocaine use.

2. Objectives
In a resource-limited setting such as Cameroon, the development and approval of such a technique could go a long way to lessen the financial burden on patients and economize resources for the hospital at large. This obviously requires proof of efficiency, which the current study sets out to determine the effectiveness and safety of IV lidocaine in rapid patient rehabilitation and procuring adequate postoperative analgesia.

3. Methods
3.1. Study Design
This was a randomized controlled trial carried out in Cameroon.

3.2. Study Setting and Population
The study was carried out over five months, from April 2017 to August 2017, at the Anaesthesiology and intensive care units (ICUs) of the Yaoundé Gynaecology, Obstetrics and Pediatrics Hospital (YGOPH), a tertiary mother and child health center in Yaoundé, the political capital of Cameroon. The study population was made up of adult (age ≥18 years) non-pregnant women classified American Society of Anesthesiologist (ASA) I and II, admitted for elective gynecological surgery (hysterectomy, myomectomy and ovarian cancer debulking surgery) under general anesthesia, who gave their informed signed consent. Patients who refused to take part in the study, those with known cardiac pathologies, and those with known allergies to lidocaine were excluded. The sample size was determined using the formula: 

\[ n = \frac{(Z/2)^2 \times P \times (1-P)}{\epsilon^2} \]

where: 
- \( n \) is the sample size, 
- \( Z \) is the standard normal variate, corresponding to 1.96 for a level of significance (α) of 0.05 and a confidence interval of 95% considered in this study. 
- \( P \) is the pre-study estimate of the prevalence of gynecology surgery at the Douala General Hospital of Cameroon which is 14.54%. 
- Q = 1 - P and \( i \) is the degree of precision we assumed to be 0.06. 

The power analysis was one. Hence, with a minimal sample size estimated at 30 patients; we needed a minimum of 15 in both groups. After validation of the research proposal and acquisition of administrative authorizations, the study began through patient recruitment. Consent was confirmed by a signature on a designed consent form.

3.3. Randomization
Patients were enrolled at the pre-anesthesia consultations where they were instructed on the use of the visual analogue scale (VAS) score for postoperative pain evaluation. They were attributed number codes ranging from RCT001 to RCT034. They were progressively drawn by sorts into 2 groups; LIDO group for those to receive IV lidocaine and PLAC group for those to receive the placebo.

Normal saline, in equivalent volumes. Both groups were matched for ASA score, the indication of the gynecological surgical procedure and their body mass indices. They were admitted to the hospital the day before surgery. We prepared the various lidocaine and placebo solutions for IV administration using an electronic pump syringe, diluting lidocaine at 4 mg/mL with saline. These syringes were labeled with patient identification numbers (RCT001-RCT034), order of passage in theatre (01–34) and a secret four-digit code to identify either placebo or lidocaine. For example, RCT001/02/XXXX. Participants’ allocation of codes was through a random sample generation of computer numbers known only to the primary investigator (RN). Hence, it was single-blind randomization. All ASA I and II women booked for an elective gynecological surgery at the study setting had equal chances to partake in this study.

3.4. Anesthesia Management
After installing each patient in the operating room in the supine position, the patient was premedicated with IV diazepam at 0.5 mg and IV atropine at 0.01 mg/kg. Then, pre-oxygenation was done followed by induction of general anesthesia using fentanyl 2 μg/kg, propofol 3-3.5 mg/kg and suxamethonium 1 mg/kg. Thereafter, endotracheal intubation was done through the oral route and patients were relayed to the anesthesia circuit where they were volume-controlled ventilated. General anesthesia was immediately maintained with isoflurane at 1%–2.5% and rocuronium at 0.6 mg/kg. Before surgical skin incision, the anesthesia team administered a bolus over one minute of either lidocaine at 1.5 mg/kg to the LIDO group or an equivalent volume of normal saline for the PLAC group. This was followed by continuous infusion for the next
6 hours of IV lidocaine at 1 mg/kg (LIDO group) or an equivalent volume of normal saline (PLAC group). Apart from the principal investigator, the rest of the anesthesia team (comprised of one anesthesiologist physician and two anesthesiologist nurses) did not know which solution (lidocaine or normal saline) was being intravenously administered to patients. The doses of fentanyl and rocuronium administered, re-injection of doses of propofol and the duration of surgery and anesthesia were noted on a pilot test-prepared data collection form on two patients not included in this study. Side effects were noted and if severe, warranted the total arrest of the lidocaine infusion for subjects in the LIDO group. Specifically, bradycardia was managed with IV atropine at 0.01 mg/kg boluses; for skin eruptions, dexamethasone was prepared at 8 mg IV boluses in case these occurred. Fifteen (15) minutes to the end of the surgery, all patients received standard analgesia with IV paracetamol 15 mg/kg over 5 minutes, and IV tramadol 100 mg. Durations for surgery (skin incision to skin closure) and anesthesia (induction of anesthesia to endotracheal extubation) were noted.

Upon endotracheal extubation, all patients were moved to the postoperative recovery room for immediate postoperative monitoring. The time-lapse from endotracheal extubation to an Aldrete score of 8 was noted. When the patient attained this score, the first VAS score was obtained. If the VAS score was greater than 3, patients immediately received 20 mg of nefopam through slow IV infusion. Postoperative analgesia was made up of paracetamol 15 mg/kg IV hourly and IV nefopam 20 mg/6 h. In case adequate analgesia (VAS score less than 3) was not achieved, tramadol was added at a dose of 100 mg/8 h, slow IV infusion. One hour after full recovery, patients were transferred to the ICU. Monitoring of the electrocardiogram (ECG) tracing, blood pressure, pulse rate and oxygen saturation through pulse oximetry was done throughout the administration of IV lidocaine or placebo for all subjects. After the first hour, patients were examined for the presence of bowel sounds through abdominal auscultation. It was repeated every hour till the 4th hour post-operation.

In the ICU, the pain was monitored at 3-hour intervals using the VAS score. Postoperative analgesia was pursued with paracetamol at 15 mg/kg every 6 hours starting 6 hours after the intra-operative dose, and IV nefopam at 20 mg/6 h. If analgesia was deemed insufficient (VAS score > 3), tramadol was administered at 100 mg IV every 8 hours. Postoperative rehabilitation measures included: early mobilization (every hour from the first hour post-operation to the fourth hour post-operation), sitting (every hour from the second hour post-operation to the eighth hour post-operation), early oral feeding 50 mL of water at the second hour, and every 30 minutes, chewing gum from the second hour (to chew for at least 15 minutes), natural fruit juice from the sixth hour, low residue meal made of pineapples and watermelon from the eighth hour), removal of the urinary catheter at the second hour (except in the case of a contraindication by the surgeon), removal of one IV line by the 24th hour, and the second before the 48th hour (latest). Tolerance of all these phases was scored on a scale from 1-3 (1 = easy, 2 = difficult, 3 = impossible) by the intensive care physician involved. The rest of the standard treatment prescribed by the ICU staff was conducted as usual (anticoagulants, antiembolism stockings, stress ulcer prevention, antibiotics, IV fluids, and blood transfusion). The lidocaine infusion was discontinued at the sixth-hour post-operation, and pain evaluation was continued till the 24th hour post-operation.

3.5. Variables

variables studied included the age, the type of intervention, the total initial bolus dose, and the total continuous perfusion dose of lidocaine, the additional doses of fentanyl, the time lapse between extubation and an Aldrete’s score of at least 8 on 10, the post-operative VAS scores, intra-and post-operative side effects of lidocaine use, time to first bowel sounds, the patient satisfaction over pain management and postoperative rehabilitation (graded 1-4), the ease with which patients were mobilized as from the second hour after surgery and every hour thereafter.

3.6. Statistical Analysis

Data analysis was done using the Epi Info version 3.5.4 software. Means were compared using chi-square test, and differences were considered statistically significant for \( P < 0.05 \). Odds ratios were used to compare outcomes. Variables were expressed as means and proportions and analyzed as such.

4. Results

The mean age of the study population was 46.35 ± 13.69 years. Women’s ages ranged from 28 to 78 years. Patients in the lidocaine group had fewer reinjections of fentanyl during surgery with a mean value of 14.70 ± 34.29 μg, compared to those in the placebo group 129.41 ± 53.20 μg (\( P < 0.001 \)). Patients in the LIDO group had a shorter recovery time compared to PLAC group (13.58 ± 4.22 minutes vs. 18.11 ± 4.38 minutes, \( P = 0.004 \)). Patients in the LIDO group reported less pain in the immediate postoperative period compared to PLAC group (mean VAS score value: 3.55 ± 2.34 cm vs. 5.44 ± 1.73, \( P = 0.012 \)). Patients in the LIDO group reported less pain on admission to the ICU compared to the PLAC group (mean VAS score: 3.55 ± 2.34 cm vs. 5.44 ± 1.73, \( P = 0.012 \)).
The occurrence of postoperative nausea and vomiting in the recovery room was similar in both groups ($P=0.300$). Concerning tolerance of early postoperative feeding, it was generally satisfactory. There was neither vomiting nor nausea after ingestion of 50 mL of water and chewing gum respectively. However, after ingestion of fruit juice at the sixth hour postoperative, four (23.5%) patients in the LIDO group and three (17.6%) in the PLAC group had nausea ($P=0.500$). On the evaluation of their management during the perioperative period, women in the LIDO group were more satisfied with pain management (mean score: $3.59 \pm 0.62$ vs. $2.94 \pm 0.05$, $P=0.001$). The same was observed for satisfaction on postoperative rehabilitation, $3.47 \pm 0.62$ for LIDO group against $2.88 \pm 0.69$ for the PLAC group ($P=0.017$). Of all the side effects of lidocaine, only bradycardia (less than 60 heartbeats per minute) was observed in 6 (35.3%) out of the 17 LIDO group. No patient in the PLAC group had bradycardia.

5. Discussion
This clinical trial sought to assess the effectiveness and safety of adjuvant perioperative IV lidocaine in procuring postoperative analgesia and early rehabilitation in gynecologic surgery. We found that adjuvant perioperative IV lidocaine statistically significantly reduced intraoperative opioid consumption, recovery time, postoperative pain, time to mobilization and increased patient postoperative satisfaction. The lone side effect of IV lidocaine was tolerable bradycardia.

VAS scores on immediate postoperative recovery, and admission to the ICU were greatly in favor of lower values in the lidocaine group compared to the placebo group. As for the evolution of these scores, patients in the lidocaine group had significantly lower pain scores up to the 12th hour, after which the differences were not significant, though lower. This is supported by the findings of a systematic review by Kranke et al in 2015, which showed conclusive evidence of the effectiveness of IV lidocaine in reducing postoperative pain. Our results also corroborate with those of Koppert et al, who demonstrated a significant decrease in pain intensity following continuous
IV administration of lidocaine in open gastrointestinal surgery. Likewise, another systematic review reported a reduction in perioperative pain when IV lidocaine infusions supplement general anesthetics.

In the present study, IV lidocaine was administered from induction of general anesthesia till the 6th postoperative hour as opposed to till the first hour in the several studies included in the systematic review by Kranke et al. This may explain why in our study, where lidocaine was used for up to 6 hours, we had less postoperative pain up till the 18th postoperative hour. Our baseline doses for lidocaine (1.5 mg/kg bolus and 1 mg/kg/h) were smaller than the doses used in many of the studies considered in Kranke and colleagues’ systematic review (bolus dose of 2 mg/kg and a maintenance dose of at 1.5 mg/kg/h). This suggests that we may have had lower pain scores and at later periods had we used higher doses. These higher doses (2 mg/kg, then 1.5 mg/kg/h are common practice and fall within the recommendation as proposed by French guidelines on the management of postoperative pain.

The use of IV lidocaine clearly showed an advantage in the recuperation of gastrointestinal function, after the second postoperative hour, almost all (16 out of 17) patients had bowel sounds present on auscultation. This falls in line with findings by Kranke et al who showed that systemic lidocaine reduced the time to first bowel movements. A recent Cochrane review confirmed an effect on reducing pain scores up to 24 hours after surgery as well as a significant reduction in risk of ileus and time to first defecation. Paralytic ileus, a common postoperative complication, has been found to exist as a result of neurogenic inflammation and the ensuing systemic inflammatory response syndrome. Early return of bowel sounds paves the way for early feeding, a key principle in the concept of fast-track surgery and rapid rehabilitation.

Irrespective of induction doses, patients in the lidocaine group had fewer reinjections of fentanyl (14 micrograms versus 129 for the placebo group). This further depicts the positive effect of IV lidocaine use on the reduction of opioid requirements, as shown by Kranke et al. The effect of the reduction of anesthetic drug requirements could also explain the reduction in immediate postoperative recovery time seen in patients who received systemic lidocaine in our study (13 minutes versus 18 minutes for the placebo group). A recent Cochrane review confirmed an effect on reducing opioid consumption (mean difference 4.52 mg morphine equivalents, 95% CI −6.25 to −2.79).

Our results show that in the perioperative period, the only observed side effect was bradycardia, observed in only 6 (35.3%) patients of the lidocaine group. Toxicity from perioperative lidocaine infusion is rare. Monitoring plasma lidocaine levels may be considered in patients at increased risk for lidocaine toxicity such as those with abnormal liver or kidney function or those who cannot be queried about symptoms of lidocaine toxicity. Jendoubi et al obtained mild or absent side effects during lidocaine infusion. Patients in both groups received 50ml of water at the 2nd hour and chewed gum straight afterward. At the sixth hour, they were given fruit juice, and at the eighth hour, a low-residue meal (fruit salad). These phases were generally well tolerated during our study irrespective of the administration of lidocaine. The use of chewing gum has proven to be effective in the occurrence of postoperative ileus, especially when associated with a little oral liquid, preferably water. The tolerance for this is favorable in our study. Many economic advantages are seen such as a reduction in hospital stay and an improvement in patient outcomes. Ileus commonly occurs after abdominal surgery, and is associated with complications and increased length of hospital stay. The current clinical trial concurs with the findings of the systematic review by Short et al, that postoperative chewing gum improves the recovery of gastrointestinal function.

Early mobilization is one of the cornerstones of enhanced rehabilitation after surgery (ERAS). A major part of our study focused on the ease with which patients could mobilize within the first 8 hours after surgery. Lidocaine showed a significant advantage in easing early mobilization. The advantages of this ease of mobilization are numerous. ERAS guidelines adopted intraoperative IV lidocaine in bowel surgery given data that it improves postoperative pain, opioid consumption, the return of bowel function, and length of hospital stay.

Patients in the lidocaine group were more satisfied with pain management and rehabilitation measures, as compared to women in the placebo group. Postoperative pain is a strong predictor of whether patients are satisfied with their perioperative care. Perioperative lidocaine infusion may be a useful analgesic adjunct in enhanced recovery protocols. Lidocaine infusion was used in enhanced recovery protocol, which showed benefits in pain scores, opioid consumption, length of hospital stay, and other outcomes. The advantages of IV lidocaine for postoperative pain are a relatively low financial cost, effective in abdominal surgeries, decreases opioid consumption, minimizes ileus, decreases hospital stay and nausea and vomiting and a decrease in the incidence of postoperative chronic pain.

5.1. Study Limitations
The study had some limitation. Firstly, the difficulty in evaluating intra-operative anesthetic gas consumption during the study. Comparing isoflurane consumption per patient would have further demonstrated the place of IV lidocaine in the reduction of consumption of anesthetic agents. Secondly, our single-blind randomization rather than the gold standard double-blind randomization of patients, has perhaps flawed our results with some selection bias. The strengths of this study include its robust study design; being a clinical trial with careful matching of the interventional group to the controlled group with good follow-up to provide solid evidence on the effectiveness and safety of adjuvant perioperative IV
Research Highlights

What Is Already Known?
- Currently, the fundamental objective of surgery is early postoperative rehabilitation through the "Fast-track" concept wherein adequate postoperative analgesia is primordial.
- It is currently recommended to adopt a multimodal analgesia regimen entailing the use of non-opioid systemic analgesics and local anesthetics such as lidocaine administered by tissue infiltration, regional blocks, or via the IV route for optimal postoperative pain management and to reduce opioid-related adverse events.
- Adjuvant IV lidocaine used for perioperative pain management and postoperative rehabilitation has been reported to procure good postoperative analgesia, preserve postoperative gastrointestinal motility and reduce perioperative consumption of opioids in high-income countries with scarce data on similar effectiveness and safety in low-and middle-income countries.

What Does This Study Add?
Adjuvant perioperative IV lidocaine used in gynecological surgery in a low-resource setting like Cameroon;
- Effectively reduces postoperative pain and perioperative consumption of opioids.
- Effectively fastens gastrointestinal and general rehabilitation, as well as patient satisfaction.
- Is associated with minimal tolerable side effects.

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Author Contributions
Conception and design of study: RN, RSBB, ALA and JZM.
Acquisition of data: RN. Analysis and interpretation of data: RN, RSBB, ALA, BJ, JMM, POE and JZM. Drafting the manuscript: RN and JNT. Revising the manuscript critically for important intellectual content: RSBB, ALA, JNT, BJ, JMM, POE and JZM. All authors read and agreed the final manuscript.

Conflict of Interest Disclosures
The authors declare that they have no conflict of interests.

Ethical Approval
Ethical clearance was obtained from the Ethical Committee of the Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon. Authorization was also sought from the Local Ethical Committee of the YGOPH. Verbal and written consent was required from participants. Patients who refused to participate in the study received their treatment without any bias. There was strict confidentiality, and all results were used for scientific purposes.

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