Research Article

Perioperative Intravenous Lidocaine is as Effective as Thoracic Epidural Analgesia in Postoperative Pain Management for Open Abdominal Surgery

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Abstract
Background: Thoracic epidural analgesia provides solid pain control after many postoperative procedures; however, it can lead to complications, has some contraindications, and occasionally fails. Intravenous lidocaine infusion has been suggested as an alternative. This trial aimed at assessing the analgesic effects of perioperative intravenous lidocaine infusion compared with thoracic epidural analgesia for open abdominal surgery. **Patients and methods**: For this open label randomized controlled study 70 patients undergoing elective abdominal surgery were randomly allocated to two groups: intravenous lidocaine group received intravenous lidocaine %2 bolus 1.5mg/kg before induction of anesthesia and then a continuous lidocaine infusion of 2mg/min until emergence then reduced postoperatively to 0.5-1mg/min and continued for 24 hours. Thoracic epidural group received 0.125% bupivacaine infusion of 5-8ml/hour from induction of anesthesia till the end of surgery then reduced postoperatively to 4-5ml/hour and continued for 24 hours. The pain scores (VAS) at rest and morphine consumption as rescue analgesic were assessed at 4, 8, 12 and 24 hours postoperatively. The incidence of postoperative complications was also recorded. **Results**: Sixty-nine patients (35 in the lidocaine group and 34 in the epidural group) were analyzed. There was not a statistically significant difference between the two groups with respect to pain scores and opioid consumption. **Conclusions**: Intravenous lidocaine was as effective as thoracic epidural analgesia in controlling postoperative pain for open abdominal surgery with opioid sparing properties.
Keywords: Thoracic epidural analgesia, intravenous lidocaine, postoperative

Introduction
Pain remains a major morbidity, influencing postoperative recovery. Postoperative pain especially after upper abdominal surgery can reduce mobility, cause pulmonary and circulatory complications, increase inflammation and delay intestinal motility[1]. Pain management in the perioperative setting involves interventions performed before, during, and after surgery that are intended to reduce or eliminate postoperative pain before discharge[2].

Multimodal pain management can achieve the best results and improve patient outcomes[3]. Opioid-sparing modalities has recently been the aim in perioperative pain management[4], due to their significant association with postoperative nausea, vomiting, delayed return in bowel function, pruritus, urinary retention, sedation[5] and respiratory depression; especially in senior patients[6] and the arising risk of becoming chronic opioid users[7].

Epidural analgesia is currently the international standard for perioperative pain management in upper abdominal surgery[8,9]. The excellent analgesic effect of epidural analgesia is clearly established, but there are several potential disadvantages; it frequently causes hypotension that may result in excessive intravenous fluid administration[10], which is particularly deleterious after bowel surgery[11]. It can also result in serious (although uncommon) complications such as epidural hematoma or abscess[12], and it has a relatively high failure rate[13]. Furthermore, epidural analgesia is contraindicated in some patients e.g. patients on certain anti-platelet therapy and patients refusing the technique.

Lidocaine has been described to have both analgesic, and anti-hyperalgesic effects, as well as anti-inflammatory properties[14]. It also accelerates the return of post-operative gastrointestinal function, which is of particular importance after major abdominal surgery[15].

Opposite to opioids, which increase the incidence of nausea and vomiting, lidocaine decreases their incidence[16].

Perioperative lidocaine infusion has been suggested as an alternative pain management modality in major abdominal surgeries. Multiple meta-analyses evaluating its efficacy found that perioperative intravenous lidocaine infusion decreases postoperative pain intensity, reduces opioid consumption, facilitates gastro-intestinal function, and shortens the length of hospital stay[17]. The risks of neurological or cardiac toxicity were not substantiated in the trials[15].

Although lidocaine infusion seems to be an effective pain management modality for open abdominal surgery[15], its effects in comparison with epidural analgesia has been investigated to a limited extent[18].

Patients and Methods

This prospective, open-label, randomized controlled trial was conducted in Assuit University Hospital in the period between January 2017 and December 2017. The Study protocol and patient consent have been approved by the local ethics committee, Faculty of Medicine, Assiut University. Clinical trials registration ID: NCT03005171

Adult patients (more than 18 years old), ASA class I-II, scheduled for open upper abdominal surgery were included. Those with contraindi-cations to thoracic epidural block e.g. bleeding diathesis and spinal cord disorders or with known allergy to local anesthetics were excluded. After obtaining written informed consent from enrolled patients; seventy patients were randomly allocated (using computer generated table) into one of two groups (35 patients in each): Epidural group: Thoracic epidural with bupivacaine infusion and Lidocaine group: Intravenous lidocaine infusion.

Procedure:

Preoperative preparation:

All patients had their upper abdominal surgery under general anesthesia with tracheal intubation. Premedications were administered to all patients in the form of antiemetic prophylaxis with 4 mg ondansetron and an anxiolytic (midazolam 20μg/Kg).

Thoracic epidural technique (in epidural group):

The epidural insertion was done under complete aseptic technique, with the patients in the sitting position. After localization of the T9-T10 or T10-T11 thoracic intervertebral space, para-median approach was used for epidural catheter placement. Lidocaine 1% was infiltrated through the skin and subcutaneous tissue. An 18 gauge epidural needle was used. Localization of the epidural space was done with the hanging drop technique. The exclusion of inadvertent intravascular or intrathecal placement was done with the injection of 3mL (1:100000) epinephrine + lidocaine. When no changes (<5 beats/min.) in the heart rate or notable lower limb numbness were detected; a 20 gauge epidural catheter was inserted to the length where 3 to 5 cm was inside the epidural space. The catheters were properly taped and secured.

Bupivacaine infusion of (0.125%) at a rate of 5-8mL/ hour was started prior to induction of anesthesia till the end of surgery then reduced to 4-5mL/ hour and continued for 24 hours postoperatively.

IV infusion of lidocaine (in lidocaine group)

An IV lidocaine bolus of (1.5 mg/kg) is given following IV line insertion, then, IV infusion of lidocaine (2%) was started prior to the induction of anesthesia at a rate of 2 to 3 mg/min till the end of surgery. Postoperatively, the infusion rate was decreased to 0.5 to 1 mg/min and continued for 24 hours postoperatively. A separate IV line was used for the infusion.

Intraoperative management:

Induction:

Following epidural placement and the start of the bupivacaine infusion (in the epidural group) and the start of the lidocaine infusion (in the lidocaine group); as described above; general anesthesia was induced using; 1-2 μg/kg fentanyl and 1.5-2mg/kg propofol. Tracheal intubation was facilitated with 0.15mg/kg cis-atracurium.

Maintenance:

Anesthesia was maintained with 1-1.5 MAC isoflurane in 50% air: oxygen mixture. Mecha-nical ventilation was adjusted to maintain end tidal CO2 between 30 and 35 mmHg. Muscle relaxation was maintained during surgery with the use of bolus doses of rocrunium, using the

train of four monitoring. Acceleromyography (TOF-Watch® S, Organon) was used to adjust the dose of muscle relaxants. Fluid maintenance was administered in the form of Ringer's

solution at a rate of 5 mL/kg/min. Blood transfusion with packed RBCs was given when hematocrit level decreased below 30%. Intraoperative analgesia in the form of 1 gm acetaminophen was given to all patients 20 minutes before skin closure.

Emergence:
At the end of surgery, all anesthetic agents were switched off, FiO2 was increased to 1.0, with the return of two twitches on train of four, reversal of muscle relaxant was given and patients were extubated.

Postoperative Management:
After emergence, all patients were transferred to the intermediate care unit where the infusions were continued as follows:
In the epidural group, 0.125% Bupivacaine infusion continued at a rate 4-5mL/hour for 24 hours postoperatively.
In the lidocaine group, 2% IV lidocaine continued at a rate 0.5 to 1 mg/min for 24 hours postoperatively. All patients were prescribed intravenous acetaminophen 1 gm every 6 hours, then oral acetaminophen 1 gm every 6 hours after the return of gastrointestinal function. Patients were administered 4mg morphine PRN (as required) as rescue analgesia whenever the pain score (VAS) reached 40 or more.

Primary outcome is pain score (visual analogue scale) as the median VAS in first 24 hours postoperatively. Secondary outcomes are opioid consumption and the incidence of complications and side effects in each group: postoperative nausea, vomiting and hypotension

Data collection
Patient characteristics and surgical data: Age, gender, weight, height, body mass index and ASA status and type of surgery. Postoperative events: hypotension, nausea and vomiting. Pain assessment data: All patients were routinely assessed by the nursing staff for pain score every 4 hours using the 100-point visual analogue scale (VAS), where zero equals no pain and 100 equals the worst pain imaginable. Opioid consumption of morphine in 24 hours

Statistical analysis
Data were represented as mean±SD, median (range) and number (%) as appropriate, independent t-test was used to compare means between parametric data, Mann-Whitney was used to compare non parametric values in the studied groups, Chi square test or fisher's exact test was used in categorical data. P-value <0.05 was considered statistically significant.

Results
During the period from December 2016 to July 2017, 110 patients were screened for participation in this study. After reviewing inclusion and exclusion criteria, 70 patients were allocated and divided randomly (using computer generated random table) into one of the two studied groups. Only one patient in the epidural group was withdrawn from the study due to failure of insertion of epidural catheter and was not included in the final data analysis.

There was no statistically significant difference between both of the studied groups regarding patients' characteristic data including age, gender, height, weight, BMI or ASA score. Regarding the type of surgery, both groups showed approximately similar proportions for each type of surgery with no statistically significant differences between both groups.

Table 1: Patients' and Surgical Data

Variable	Lidocaine Group	Epidural Group	P-value
Age (years)	43.8 ± 12.7	44.8 ± 12.1	0.741
Gender			
• **Female**	23 (65.7%)	22 (64.7%)	0.565
• **Male**	12 (34.3%)	12 (35.3%)	
Height (cm)	164.4 ± 7.9	164.1 ± 9.3	0.892
Weight (kg)	71.1 ± 10.1	72.2 ± 10.3	0.675
BMI (kg/m^2)	26.3 ± 3.3	26.8 ± 3.5	0.792
ASA classification			
• **I**	19 (54.3%)	19 (55.9%)	0.543
• **II**	16 (45.7%)	15 (44.1%)	
Type of surgery (%)			
CBD Exploration	6 (17.1%)	6 (17.1%)	0.590
Cholecystectomy	14 (40%)	14 (40%)	
Diaphragmatic Hernia	0 (0%)	0 (0%)	
Epigastric Hernia	8 (22.9%)	8 (22.9%)	
Exploration	3 (8.6%)	3 (8.6%)	
Incisional Hernia	1 (2.9%)	1 (2.9%)	
Whipple	3 (8.6%)	3 (8.6%)	
Data presented as mean±SD and number (%)			

Pain scores and analgesic requirements: The intensity of pain was measured at rest using VAS in the 4th, 8th, 12th, and 24th hours postoperatively. There was no statistically significant difference between the two groups at any of the measured times. Four patients in lidocaine group requested additional opioid analgesia during the first 24 hours (in the form of 4 mg morphine), compared to only one patient in the epidural group. Statistical analysis revealed no significant difference between both groups. Table 2

Table 2: Pain Scores and Analgesia Requirements

VAS	Lidocaine Group	Epidural Group	P-value
After 4 hours	20.03 ± 0.51	10.91 ± 0.57	0.242
After 8 hours	20.11 ± 0.83	10.82 ± 0.63	0.168
After 12 hours	10.91 ± 0.56	10.79 ± 0.59	0.376
After 24 hours	10.71 ± 0.62	10.62 ± 0.49	0.599
Median in 24 hours	10.94 ± 0.4	10.74 ± 0.46	0.122
Maximum	20.43 ± 0.65	20.18 ± 0.58	0.105
Opioid requirement; n(%)	4 (11.4%)	1 (2.9%)	0.356
Data presented as mean±SD and number (%)			

Postoperative complications were reported as hypotension, bradycardia, nausea and vomiting. Postoperative hypotension occurred in 4 patients in the epidural group. No patients developed postoperative hypotension in the lidocaine group, but this difference did not reach the significance level.

Postoperative nausea occurred in 4 patients in the lidocaine group and in 9 patients in the epidural group with no significant difference between both groups. Like nausea, post-operative vomiting showed higher incidence in epidural group 14.7% compared to 5.7% in lidocaine group, however, with no statistically significant difference. Table 3

Table 3: Postoperative Events

Variable	Lidocaine Group	Epidural Group	P-value
Hypotension; n (%)	0 (0.0)	4 (11.8)	0.540
Bradycardia; n (%)	0 (0.0)	2 (5.9)	0.239
Nausea; n (%)	4 (11.4)	9 (26.5)	0.133
Vomiting; n (%)	2 (5.7)	5 (14.7)	0.259
Data presented as number (%)			

Discussion

This randomized controlled clinical trial was conducted to compare between the efficacy of epidural analgesia and intravenous lidocaine infusion as a systemic analgesic agent in upper abdominal surgery.

The results of this study showed that both techniques were comparable to each other as regard the analgesic effect in terms of VAS and postoperative opioid consumption.

Even though there are several studies investigating the effects of intravenous lidocaine on postoperative analgesia and ileus duration, the literature regarding comparisons with epidural analgesia in patients undergoing major abdominal surgery is quite limited[19].

Swenson et al.,[20] conducted a small prospective, randomized clinical trial comparing thoracic epidural analgesia (20 patients) to intravenous lidocaine (22 patients) in open colon surgery patients. They used TEA (bupivacaine 0.125% and hydromorphone 6 Kg/mL) that was started at 10 mL/hour within 1 hour of the end of surgery) and intravenous lidocaine (1 mg/min in patients <70 kg, 2 mg/min in patients ≥70 kg). In agreement with the findings of the present study, they found no statistically significant differences between the two groups in pain scores, analgesic consumption, time to return of bowel function or hospital length of stay. Wongyingsinn et al.,[21] conducted a another prospective, randomized clinical trial comparing thoracic epidural analgesia (30 patients) to intravenous lidocaine (30 patients) in in patients undergoing laparoscopic colorectal resection. Their primary outcome was time to return of bowel function; which was similar in both groups. Thoracic epidural infusion was started before induction of anesthesia at a rate of 5 to 8 mL/hour of bupivacaine 0.25% intraoperative; this concentration is higher than the one used in this study. Postoperatively, they used bupivacaine 0.1% and morphine 0.02 mg/mL. Intravenous lidocaine infusion was started before induction of anesthesia at a rate of 2 mg/kg per hour intraoperative; then decreased to 1 mg/kg/hour in the postoperative period. Infusions continued for 48 hours after surgery. The overall quality of analgesia was similar in those patients undergoing colonic resection; however, it was not the case in patients with rectal resection. They explained their findings by the fact that the group with rectal anastomosis had larger incisions with greater nociception, than the other group.

A few years later, in 2016, Terkawi et al.,[18] conducted a larger (two hundred sixteen patient) retrospective, nonrandomized, non-inferiority trial comparing thoracic epidural analgesia to intravenous lidocaine in patients undergoing major abdominal surgery. Their results were consistent with findings of the present study and stated that intravenous lidocaine was not inferior to epidural analgesia with respect to pain scores. They used the same rate of infusion as that used in this study, however for a longer duration postoperatively (4days).

Lidocaine has multiple mechanisms of action. It blocks sodium channels in the neuronal cell membrane that may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain[22]. Lidocaine is believed to have analgesic,[14] and antihyperalgesic properties by reducing secondary hyperalgesia through a central mode of action[23]. Systemic administration of lidocaine inhibits the activation of human N-methyl-D- aspartate glutamate receptors in a concentration-dependent fashion, which may contribute to reduced hyperalgesia and opiate tolerance[24]. Lidocaine has also been found to block

neutrophil accumulation at the injury site and reduce the release of inflammatory mediators that may account for significant anti-inflammatory properties[25].

The results of the current study are consistent with the findings of other researchers who affirmed that systemic lidocaine is deemed effective in postoperative pain reduction following abdominal surgery[26]. However, when its analgesic effect was studied in types of surgeries, other than abdominal, the results were variable[27-29].

Intravenous lidocaine infusion seems to have a specific effect on visceral pain sensation. Animal studies have demonstrated that lidocaine causes a dose-dependent inhibition of visceromotor reflexes and reduction in evoked and spontaneous neuronal activity arising from bowel distension. This visceral-specific effect may explain the good analgesic properties of systemic lidocaine after bowel surgery with rather less effect in non-abdominal surgeries[30].

The debate about the efficacy of intravenous lidocaine as postoperative analgesia is still present. In the last two years, four meta-analyses investigated the use of intravenous lidocaine infusion in postoperative pain control, with different inclusion and exclusion criteria and outcome measures, with surprisingly inconsistent conclusions. In 2016 Weibel et al.,[31] who included 2802 patients from forty-five trials in their meta-analysis showed limited evidence of positive effects of lidocaine on postoperative gastrointestinal recovery, opioid requirements, postoperative nausea and vomiting, and length of hospital stay. MacFater et al.,[32] in their meta-analysis published in 2017 reached nearly the same conclusion about IV lidocaine in colorectal surgery; they found that IV lidocaine has shown only limited benefit towards reducing early postoperative pain and morphine consumption when compared with placebo.

On the other hand, Ventham et al., in 2015[33] conducted a meta-analysis containing fourteen RCTs with 742 patients. From this meta-analysis the authors concluded that IV lidocaine has a multidimensional effect on the quality of recovery, moreover; IV lidocaine was associated with lower opiate requirements, reduced nausea and vomiting and a shorter time until resumption of diet. Khan et al., in 2016 affirmed the analgesic or gastrointestinal benefits of IV lidocaine following bowel surgery. However, tried to estimate the appropriate end time for an intraoperative intravenous lidocaine infusion[34].

This study has some limitations. First, the study was not blinded, and this may have influenced the results. However, it is considered that blinding of an epidural infusion would have been very difficult, if not impossible, therefore true blinding would have been unlikely to be maintained even if attempted. Moreover, if any placebo effect influenced the present results, it would have been expected to be in favor of the more interventional approach, that is, the epidural therapy.

Secondly, two different local anesthetics were used: bupivacaine for epidural administration and lidocaine for intravenous administration. The reasons for this choice were to mimic as closely as possible the clinical setting. Bupivacaine is a standard drug for epidural therapy, and lidocaine would not be suitable in that setting. Conversely, bupivacaine is not suitable for IV administration because of its cardiotoxic effects. Because considerable data support the effectiveness of IV administration of lidocaine, and because in previous laboratory investigations there was very similar anti-inflammatory effects of bupivacaine and lidocaine[35], hence the choice to use different drugs for the two administration modes.

Third limitation is that the lidocaine concentrations were not analyzed in the allocated patients. The check of plasma concentration would have improved the understanding of the relationship between the pharmacokinetics of this drug and its systemic and side effects, However, both the dose and the duration of lidocaine treatment used in the current study have been described to be effective in other clinical trials[18].

Moreover, the used regime was of smaller dosage and a shorter duration of lidocaine infusion than that used in previous studies[36] in which the lidocaine did not reach a toxic concentration and in which there were no side effects reported. In the present study, no patients showed signs of lidocaine toxicity.

The fourth limitation is concerning the variety of the upper abdominal surgeries included in the study, which ranged from moderate to complex surgeries. Unfortunately the sample size was not sufficiently large to evaluate interaction, i.e., whether or not the effect of lidocaine differs with different magnitude or types of upper abdominal surgeries. However, the different types of surgeries were randomly distributed between both groups, with no statistically significant difference, which should not have affected the results.

Lastly, in the present study, all patients received postoperative IV paracetamol 1gm/ 6 hours as following our institution's protocol for multimodal postoperative analgesia. However patients in both groups received the same regime, which would not have affected the results of this comparative study. On the other hand, this might have been the reason for the overall lower pain scores in the current study, compared to the pain scores recorded in previous ones.

Conclusion

From the findings of the present study, intravenous lidocaine infusion can provide postoperative analgesia comparable to that of thoracic epidural analgesia for open abdominal surgery. Thus, it can be used as an alternative to the more invasive thoracic epidural analgesia for the control of postoperative pain in patients undergoing upper abdominal surgery. Also, this study suggests that in patients with contraindications or presenting difficulty for epidural insertion, intravenous lidocaine infusion is a feasible substitute. However, further studies and investigations are required to support this conclusion and suggestion. Also, more studies are recommended to determine the optimal dose and duration for perioperative intravenous lidocaine infusion.

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