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Intraoperative infusion of lidocaine 2% reduces postoperative fentanyl requirements for pain control in renal transplantation surgery

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Abstract

Background: Intravenous lidocaine has been shown to be an analgesic and anti-inflammatory medication with modulation of excessive inflammatory response.

We investigated the efficacy of intraoperative lidocaine 2% infusion in reducing the postoperative Fentanyl requirements for analgesia in renal transplant recipients. Patients were assigned equally into two groups by computer-generated list compiled before the start of the study. Control group: fentanyl (F) group and study group: lidocaine 2% (L) group. Medication used is either lidocaine in the dose of 2 mg/kg/h and the other syringe contained saline both have been infused by rate of 10 ml/h. Fentanyl induction dose given for the two groups was 1.5 mcg/kg. Both groups have received extra fentanyl according to their intraoperative analgesic requirements, patients in the lidocaine group received the fentanyl induction dose accompanied by lidocaine 2% 1.5 mg/kg as loading dose, followed by maintenance dose of lidocaine 2% infusion 2 mg/kg/h. After transfer to the PACU nursing staff administered fentanyl 0.5 mcg/kg boluses for postoperative pain relief every 10 min up to 2 mcg/kg, the recovery nurse used the pain numerical score to assess pain. The recovery nurse referred the patient to the responsible anesthesiologist covering the recovery unit if he required more than 2 mcg/kg of fentanyl to control postoperative pain. Patient was then transferred to the RTU (renal transplant unit), postoperative pain and fentanyl PCA consumption were followed up during the first 24 h.

Results: Our study detected increased fentanyl consumption in the recovery for the fentanyl group more than the lidocaine group. The request of the first dose of analgesic was significantly longer in lidocaine group than in fentanyl group.

Conclusion: The usage of intraoperative lidocaine infusion decreased postoperative fentanyl requirements as analgesic in patients undergoing renal transplantation.

Trial registration: Registration on ANZCTR number [ACTRN12618001335280](https://www.anzctr.org.au/Trial/Registration/Trial.jsp?ACTRN12618001335280), REGISTERED 08 August 2018.

Keywords: Lidocaine 2% infusion, Fentanyl, Postoperative pain, Anesthesia for renal transplantation

Background

Nausea, vomiting, paralytic ileus, postoperative pain, and cognitive dysfunction are some problems that face the recipients of renal transplantation surgery. The postoperative pain is explained as inflammatory reaction with local and

systemic response and as neuropathic pain that occurs after damaged nerve fibers that lowers the threshold to pain (Hollmann and Durieux 2000). Fentanyl given either through intravenous or through patient control analgesia (PCA) aimed to reduce the postoperative pain but is still associated with complications such as nausea, constipation, respiratory depression (Rimback et al. 1990). The target is to avoid the complications of fentanyl by using alternatives that add to analgesics without exaggerating the side effects

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(Koppert et al. 2004). Intravenous lidocaine has been shown to be an analgesic and anti-inflammatory medication with modulation of excessive inflammatory response. These properties are mediated by a variety of mechanisms, including sodium channel blockade, as well as inhibition of G protein-coupled receptors and N-methyl-D-aspartate receptors (Hollmann and Durieux 2000; Hollmann et al. 2005; Nagy and Woolf 1996; Sugimoto et al. 2003; Cassuto et al. 2005). The effect is thought to reflect the inhibition of primary evoked polysynaptic reflexes in the spinal dorsal horn mediated by a variety of mechanisms including sodium channel blockade (Pypendop and Ilkiw 2005).

Methods

The aim

We aimed in studying the efficacy of intraoperative lidocaine 2% infusion in reducing the postoperative fentanyl requirements for analgesia in renal transplant recipients.

Design and settings of the study

After the approval of ethical committee of the hospital and research center on 11/02/2019 with REF: RC-J/262/40, the study was conducted between February 2019 and July 2019. Simple randomization was done using computer-generated random numbers. Sample size calculation revealed that at least 25 patients are needed in each group to detect a difference of at least 50 mcg in the average consumption of opioid in the recovery, with significant level of 0.05 and a power of 0.9. It is a double blinded study depending on two anesthetists; one anesthetist was responsible for the preparation of the medication in 50 ml syringe to be infused by syringe pump during the procedure, medication is either lidocaine by the dose of 2 mg/kg/h and the other syringe contained saline both have been infused by rate of 10 ml/h, the other anesthetist which infused the medication and was not aware about the nature of the infused medication. Inclusion criteria included recipients for renal transplantation surgery within 16 to 60 years old, ASA III patients. Patients with history of liver cell failure, heart failure, chronic use of opioids, and allergy to either lidocaine 2% or fentanyl were excluded from the study. Patients were randomly assigned equally into 2 groups by computer-generated list compiled before the start of the study. Control group: fentanyl (F)

group and study group: lidocaine 2% (L) group. Patients did dialysis session one day before surgery. In the preoperative visit, the patient had a full discussion about the study and medications used with explanation about fentanyl PCA—patient-controlled analgesia—and how to use it postoperatively. Patient signed the study's consent and the anesthesia consent. On arrival of the patient to the operating theatre, baseline values of heart rate, oxygen saturation, and non-invasive blood pressure were recorded. Patients were pre-medicated by midazolam 0.03 mg/kg IV in the induction area with maximum dose of 2 mg. Anesthesia was induced by propofol 1.5–2.5 mg/kg IV, regarding the fentanyl induction dose given for the two groups; both groups were received 1.5 mcg/kg. Patients in the fentanyl group received fentanyl according to their intraoperative requirements, patients in the lidocaine group received only the fentanyl induction dose accompanied by lidocaine 2% 1.5 mg/kg as loading dose, followed by maintenance dose of lidocaine 2% infusion 2 mg/kg/h. Patients were intubated by oral endotracheal tube using atracurium as muscle relaxant with intubation dose 0.5 mg/kg IV, and incremental doses 0.1 mg/kg monitored by train of four neuromuscular monitor. Anesthesia was maintained with sevoflurane with end tidal concentration adjusted to keep BIS value between 35 and 50 and to maintain heart rate and mean arterial blood pressure within 20% of the baseline value. Patients were ventilated with mixture of oxygen and air (Fi O₂ 40%) adjusted to keep O₂ saturation between 95 and 100% with minute ventilation to maintain carbon dioxide (CO₂) between 35 and 45 mmHg. Temperature was monitored by nasal temperature probe to maintain patient temperature between 36 and 37°C. Post-induction, invasive blood pressure was monitored by 20-gauge cannula inserted in the radial artery on the nondependent hand or the hand with no arteriovenous fistula. Central venous catheter was inserted ultrasound guided for central venous pressure (CVP) monitoring. All surgeries were performed by two surgeons. Patient received antibiotics within 30 min before skin incision, with methyl prednisolone 250 mg and immune suppressive medications (basiliximab or anti thymocyte globulin), intravenous paracetamol 1000 mg, and diphenhydramine 12.5 mg as recommended by the nephrology team. Patient received granisteron 1 mg 15 min before skin closure.

Table 1 Patient's characteristics

Type of patients	No. of patients	Body weight in kg: mean ± SD	p value
Lidocaine group	25	69.92 ± 12.052	0.601
Fentanyl group	25	67.44 ± 20.183	
Type of patients	No. of patients	Age in years: mean ± SD	p value
Lidocaine group	25	38.80 ± 11.489	0.098
Fentanyl group	25	43.72 ± 8.970	

Both groups were comparable with regard to age and weight. The type and lengths of the surgical procedures were similar (150–180 min); there was no perioperative mortality among the 50 patients enrolled in our study.

Table 2 First 24 h demand of postoperative controlled analgesia (PCA)

Type of patients	No. of patients	No. of demands attempts: mean \pm SD	<i>p</i> value
Lidocaine group	25	74.24 \pm 40.882	0.235
Fentanyl group	25	61.00 \pm 36.860	
Type of patients	No. of patients	No. of PCA doses given: mean \pm SD	<i>p</i> value
Lidocaine group	25	36.76 \pm 14.895	0.954
Fentanyl group	25	36.52 \pm 14.336	

PCA fentanyl – 1 ml (10 μ g) per dose with lockout 10 min provided adequate analgesia in both groups in the first 24 h postoperative: the pain intensity at rest was not different between groups, with a median pain intensity score not exceeding 1 of 10 (*p* value 0.235), there was no significant difference between the two groups regarding the PCA demands and the PCA doses given to the two groups, fentanyl group required average of 61 \pm 36.8 attempts with 36.52 \pm 14.336 PCA doses supplied in comparison to the lidocaine group which required 74.24 \pm 40.88 PCA doses and supplied by 36.67 \pm 14.895 PCA doses with *p* value of 0.954

Lidocaine infusion stopped with the beginning of skin closure. Episodes of hypotension (decreased systolic blood pressure more than 20% of the baseline) were managed by phenylephrine increments, episodes of bradycardia (decreased heart rate that caused hypotension and affected patient's hemodynamics) were managed by Atropine. Average intraoperative crystalloid was 35–50 ml/kg. Neuromuscular block was reversed by neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV. Patients were extubated, then transferred to the recovery (PACU) to stay for 1 h before transfer to the renal transplant unit (RTU). The time of surgery was 150–180 min and it was done by the same team of renal transplantation surgeons. In the PACU, the blood pressure, heart rate, respiration, and temperature were monitored and recorded by nurses who were blinded to the randomization sequence. According to study protocol, the PACU nursing staff administered fentanyl 0.5 mcg/kg boluses for postoperative pain relief every 10 min, if patient complained of pain, up to 2 mcg/kg, if the patient required more fentanyl to keep Numerical pain score less than 4, the nurse called the anesthetist responsible for the recovery for assessment and to give extra doses accordingly, until the patient was able to use the fentanyl patient-controlled analgesia (PCA). The PCA machine adjusted to give 10 mcg of fentanyl with lockout of 10 min. Pain was assessed by numerical pain score (0–10 scale, where 0 = no pain, and 10 = excruciating pain). The nurses evaluated the patients every 5 min or at the patient's request. After 1 h in the PACU, patient was then transferred to the renal transplant unit (RTU), where postoperative pain and fentanyl PCA consumption were followed up during the first 24 h. Primary

outcome: reduction of postoperative fentanyl requirements for the pain control, secondary outcome: intraoperative fentanyl requirements.

Results

Fifty patients were allocated into two groups fentanyl group no. 25, lidocaine group no. 25, each group consist of 25 patients (Table 1). There were no cases excluded from the study. Data were collected, coded, tabulated, and then analyzed using SPSS® 16.0 statistical package. Variables were presented as mean and standard deviation and analyzed using unpaired *t* test. Any difference with *p* value < 0.05 was considered statistically significant. Sample size calculation revealed that at least 25 patients are needed in each group to detect a difference of at least 50 mcg in the average consumption of opioid in the recovery, with significant level of 0.05, and a power of 0.9.

Discussion

In the immediate postoperative setting following kidney transplant, analgesia is usually delivered via patient-controlled analgesia (PCA) during the initial 24–48 h. Use of the PCA administrative technique has been shown to improve pain control, reduce opioid-related complications such as sedation and improve patient satisfaction (Momeni et al. 2006). Recovery after kidney transplant may be delayed with postoperative ileus, a complication exacerbated by the use of opioids (McMillan 2004) in addition a high intraoperative opioid consumption is largely associated with

Table 3 Time required for the first dose in the recovery/consumption of fentanyl in the recovery

Type of patients	No. of patients	Time in min: mean \pm SD	<i>p</i> value
Lidocaine group	25	45.88 min \pm 19.404 min	< 0.001
Fentanyl group	25	14.64 min \pm 4.281 min	
Type of patients	No. of patients	Fentanyl consumption in microgram: mean \pm SD	<i>p</i> value
Lidocaine group	25	43.87 μ g \pm 26 μ g	< 0.001
Fentanyl group	25	116.96 μ g \pm 37.92 μ g	

Analgesic requirements: the mean time for the request of the first dose of analgesic was significantly longer in lidocaine group than in fentanyl group (45.88 \pm 19.404 vs 14.64 \pm 4.281 with *p* value of < 0.001). There was a statistically significant difference between the 2 groups with *p* value < 0.001, increased fentanyl consumption in the recovery for postoperative analgesia in the fentanyl group (116.96 μ g \pm 37.92 μ g) more than the consumption in the lidocaine group (26 μ g \pm 43.87 μ g)

Table 4 Numerical pain score in the recovery

Type of patients	No. of patients	No. of patients with numerical pain score more than 4 in the first hour in the recovery: mean \pm SD	<i>p</i> value
Lidocaine group	25	2.64 \pm 2.481	< 0.001
Fentanyl group	25	6.68 \pm 1.345	

Intensity of pain assessed in PACU, the mean pain numerical pain score in lidocaine group remained significantly less than that in the fentanyl group ($p < 0.001$) in the first hour

higher analgesic consumption in the postoperative period, prolonged sedation, ileus, urinary retention, and prolonged length of hospital stay (Bakan et al. 2015).

We tried to examine the efficacy of intraoperative lidocaine infusion in reducing the postoperative fentanyl requirements for renal transplant recipients, we found that it significantly reduced the fentanyl requirements both intraoperative and early postoperative in the recovery yet this effect did not last so long as the 24 h postoperative requirements of fentanyl was nearly the same in both groups a condition which may be related to the short duration of action of lidocaine (Table 2).

Perioperative lidocaine infusion was found to be an effective analgesic modality in the study of Baral et al. who assessed the effectiveness of perioperative intravenous lidocaine infusion on postoperative pain intensity and analgesic requirement in 60 patients undergoing major upper abdominal surgery where 30 patients received lidocaine 2.0% (intravenous bolus 1.5 mg/kg followed by an infusion of 1.5 mg/kg/h), and 30 patients received normal saline. Postoperative pain intensity and analgesic (diclofenac) requirement were assessed at the interval 15 min for 1 h then 4 hourly up to 24 h. The pain intensity at rest and movement as well as the total postoperative analgesic (diclofenac) requirement were significantly lower in lidocaine group; the extubation time was significantly longer in lidocaine group and the time for the first dose of analgesic requirement was longer in lidocaine group (Baral et al. 2010) (Table 3).

In 2008, Marret et al. did a retrospective analysis of 8 trial including 161 patients who received perioperative lidocaine infusion and they found that intravenous lidocaine administration decreased the duration of ileus, length of hospital stay, postoperative pain intensity at 24 h after operation on a visual analog scale and the incidence of nausea and vomiting (Marret et al. 2008) (Table 4).

Nearly the same findings were found by McCarthy et al. who performed a systematic review of randomized

controlled comparisons of lidocaine infusion with placebo in the surgical setting and reporting on postoperative analgesia and other aspects of patient recovery from surgery from 1966 to 2009. Sixteen trials were included, a total of 395 patients received intravenous lidocaine with 369 controls. In open and laparoscopic abdominal surgery, as well as in ambulatory surgery patients, intravenous perioperative infusion of lidocaine resulted in significant reductions in postoperative pain intensity and opioid consumption. Pain scores were reduced at rest and with cough or movement for up to 48 h postoperatively. Opioid consumption was reduced by up to 85% in lidocaine-treated patients when compared with controls. Infusion of lidocaine also resulted in earlier return of bowel function, allowing for earlier rehabilitation and shorter duration of hospital stay (McCarthy et al. 2010).

AbdelRady et al. examined 40 patients undergoing spinal fusion surgery who were randomized into 2 equal groups. Patients in the lidocaine group received IV lidocaine at a dosage of 2.0 mg/kg slowly before induction of anesthesia, followed by lidocaine IV infusion at a rate of 3.0 mg/kg/h until the end of surgery. Patients in the control group received an equal volume of normal saline. Lidocaine significantly reduced the postoperative pain score (VAS) for up to 3 months, significantly reduced morphine consumption in the first 24 h postoperative and also significantly prolonged the time to first request for additional analgesia (Ibrahim et al. 2018).

Soo Joo et al. had findings opposite to our study; they examined the effect of lidocaine infusion on the bowel function and pain intensity in 60 female patients after breast surgery who were equally divided to two groups. One group received a 1.5 mg/kg bolus of lidocaine approximately 30 min before incision followed by continuous infusion of lidocaine (1.5 mg/kg/h) until skin closure (lidocaine group). The other group was untreated (control group). Intraoperative lidocaine infusion reduced by 5% the amount of sevoflurane required at similar bispectral index ($p = 0.014$). However, there were no

Table 5 Intraoperative end-tidal concentration of sevoflurane

Type of patient	No. of patients	Sevoflurane end-tidal concentration: mean \pm SD	<i>p</i> value
Lidocaine group	25	1.700 \pm 0.2500	< 0.001
Fentanyl group	25	2.640 \pm 0.4899	

The consumption of sevoflurane inhalational gas used for anesthesia maintenance decreased in the lidocaine group with lower end-tidal concentration (1.700 \pm 0.2500) in comparison to the fentanyl group (2.640 \pm 0.4899). There was statically significance relation between the two groups with p value < 0.001

Table 6 Preoperative (heart rate HR and mean blood pressure MBP)/intraoperative (heart rate HR and mean blood pressure MBP)/recovery (heart rate HR and mean blood pressure MBP)

Type of patients	No. of patients	Preoperative HR (b/min): mean \pm SD	p value
Lidocaine group	25	82.32 \pm 6.908	0.032
Fentanyl group	25	86.28 \pm 5.675	
Type of patient	No. of patients	Preoperative MBP (mmhg): mean \pm SD	p value
Lidocaine group	25	96.44 \pm 6.777	0.001
Fentanyl group	25	103.28 \pm 6.478	
Type of patient	No. of patients	Intraoperative HR (b/min): mean \pm SD	p value
Lidocaine group	25	61.92 \pm 6.075	<0.001
Fentanyl group	25	89.32 \pm 5.907	
Type of patients	No. of patients	Intraoperative MBP (mmhg): mean \pm SD	p value
Lidocaine group	25	74.28 \pm 6.655	< 0.001
Fentanyl group	25	104.08 \pm 7.182	
Type of patients	No. of patients	Recovery HR (b/min): mean \pm SD	p value
Lidocaine group	25	73.32 \pm 7.169	< 0.001
Fentanyl group	25	111.12 \pm 6.597	
Type of patients	No. of patients	Recovery MBP (mmhg): mean \pm SD	p value
Lidocaine group	25	74.28 \pm 6.655	< 0.001
Fentanyl group	25	107.64 \pm 7.979	

Preoperative hemodynamics measurement (regarding heart rate and mean blood pressure) showed no significant difference between the two groups. Overall, the mean intraoperative heart rate and MAP in the fentanyl group remained significantly higher statistically during the entire infusion period than that in the lidocaine group ($p < 0.001$) but within clinically acceptable range. During the recovery period, heart rate and Mean blood pressure showed higher levels in fentanyl group in comparison to lidocaine group with significant difference of p value < 0.001 .

significant effects of lidocaine regarding the return of bowel function, postoperative pain intensity, analgesic sparing and side effects at all time points, hospital stay, and level of patient's satisfaction for pain control. They related the cause of their findings to the slightly lower dose of lidocaine used in their study (Choi et al. 2012).

This was similar to the results of Martin et al. who examined the analgesic effect of lidocaine after total hip arthroplasty on 60 patients divided into two equal groups. Thirty patients received lidocaine 1% with a 1.5 mg/kg IV bolus in 10 min followed by a 1.5 mg/kg/h IV infusion and other patients received saline. These regimens were started 30 min before surgical incision and stopped 1 h after skin closure. Lidocaine blood concentrations were measured at the end of administration. In both groups, postoperative analgesia was provided exclusively by patient-controlled IV morphine. They found that lidocaine did not induce any opioid-sparing effect during the first 24 h (-2 mg with 95 CI $[-5; 9]$; $p = 0.55$). There was no significant difference regarding the effects of lidocaine and placebo on pain score, pressure pain thresholds, extent in the area of hyperalgesia, and maximal degree of active hip flexion tolerated. They also attributed the reason of their results to the low dose of lidocaine use and the possible need of a larger sample size (Martin et al. 2008).

In our study, lidocaine infusion reduced the intraoperative inhalational anesthetic requirements by 25%, and this was similar to the findings of Soo

et al. who reported a reduced intraoperative sevoflurane usage by 5% (Table 5).

Patients in the lidocaine group showed more controlled heart rate and mean blood pressure with less fluctuations than the fentanyl group which showed increase in intraoperative heart rate and mean blood pressure due to pain which was controlled by boluses intravenous fentanyl (Table 6). This was similar to the results of BK Baral et al. Also, patients in the lidocaine group had better controlled heart rate and arterial blood pressure all through the first hour postoperatively reflecting the efficacy of lidocaine infusion in blunting the stress response in the short postoperative period.

Conclusion

The intraoperative usage of lidocaine 2% infusion decreased the fentanyl requirements in the intraoperative and postoperative period with decrease in the sevoflurane requirements for Anesthesia maintenance.

Abbreviations

F: Fentanyl; L: Lidocaine; PCA: Patient-controlled analgesia; FiO₂: Fraction of inspired oxygen; CO₂s: Carbon dioxide; CVP: Central venous pressure; PACU: Postoperative care unit; RTU: Renal transplant unit; HR: Heart rate; MBP: Mean blood pressure

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Authors' contributions

MKA is responsible for data collection, data analysis, writing manuscript. THI is responsible for data collection and help in writing manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

All data and material are available on the main manuscript and additional information will be provided upon request.

Ethics approval and consent to participate

After approval of the institutional ethical committee of King Faisal Specialized Hospital and Research Center on 11/02/2019 with REF: RC-J/262/40 and patient was consented by written concept for participation in the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests regarding the publication of this paper. We have not published or submitted any related papers from the same study.

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