**Intraoperative infusion of Lidocaine 2% reduces postoperative Fentanyl requirements for postoperative pain control on patients undergoing renal transplantation.**

**Introduction**

There are common problems that face the patient undergoing renal transplantation include nausea, vomiting, paralytic ileus, postoperative pain and cognitive dysfunction. Opioids given either through intravenous or through patient control analgesia (PCA) aimed to reduce the postoperative pain yet still associated with opioid complications such as nausea, constipation, respiratory distress. 1 The target is to avoid the complications of opioids using alternatives that add to analgesia without exaggerating the side effects.2 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.3 Lidocaine has shown analgesic and anti-inflammatory properties .4

**Aim of the study**

The usage of intraoperative lidocaine 2% infusion reduces postoperative opioid requirements during renal transplantation surgery.

**Material and methods**

After the approval of ethical committee of King Faisal specialized hospital and Research Center the study was conducted between December 2016 and September 2017. Inclusion criteria includes recipients for renal transplantation surgery within age more than 16 years old up to 70 years old, they did dialysis session one day before surgery, patients received their antihypertensive medications preoperative and ASA III patients. Exclusion criteria history of liver cell failure, heart failure, chronic use of opioids, and allergy to the used medications either lidocaine 2% or fentanyl and inability to comprehended pain. Fifty patients were randomly scheduled and divided equally into 2 groups: Control group: Fentanyl (F) group and study group: lidocaine 2% (L) group. On arrival of the patient to the operating theatre, and baseline values of heart rate, oxygen saturation, non-invasive blood pressure were recorded. Patients received instructions about fentanyl PCA -(patient controlled analgesia)- and how to use postoperatively, patients were pre medicated by midazolam 0.03mg/kg IV in the induction area with maximum dose of 2 mg. Induction of anesthesia started by Propofol 1.5- 2.5mg/kg IV, regarding the Fentanyl: for the control group ( fentanyl group) patient received 3 ug/kg through the whole procedure, regarding the lidocaine group: they received fentanyl 1.5 ug/kg with loading dose of lidocaine 2% 1.5 mg/kg followed by maintenance dose 2mg/kg/hr in the form of infusion started with the induction. Patient intubated by oral endotracheal tube using Atracrium as muscle relaxant with intubation dose 0.5 mg/kg IV, and incremental doses 0.1mg/kg monitored by train of four neuromuscular monitor. Anesthesia was maintained with sevoflurane (inhalational gas) 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. The mechanical ventilation with mixture of oxygen and air (Fi O2 40%) adjusted to keep O2 saturation between 95%-100%with minute ventilation to maintain CO2 between 35 and 45 mmHg. No supplemental fentanyl was given to patients in either group during maintenance of anesthesia. Temperature monitoring by nasal temperature probe to maintain patient temperature between 35-37 degree Celsius. Post induction, invasive blood pressure monitoring by 20 gauge cannula inserted in the radial artery on the nondependent hand or the hand with no arteriovenous fistula for dialysis. Central venous line inserted ultrasound guided, central venous pressure (CVP) monitoring will be measured continuously. All surgeries were performed by two surgeons who were highly experienced in renal transplantation surgery. Patient received antibiotics after induction within 30 minutes before skin incision, with methyl prednisolone 250 mg, infusion of immune suppressive medications (Basiliximab or Anti Thymocyte globulin), intravenous paracetamol 1000 mg and Diphenhydramine 12.5 mg as the recommendations by the nephrology team responsible for renal transplantation in our institute. Patient received Granisteron 1 mg 15 minutes before skin closure, as antiemetic medication. Lidocaine infusion stopped with the beginning of skin closure. Episodes of hypotension occurred with any group were managed by Phenylepherine increments, episodes of bradycardia occurred with any group were managed by Atropine. Infusion of crystalloids intraoperatively done with the surgeon recommendations, mostly infusion of crystalloids was 35-50 ml/kg. Neuromuscular block was antagonized with neostigmine 0.05mg/kg and glycopyrrolate 0.01 mg/kg IV. Patients were transferred to the PACU where the blood pressure, pulse, 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 25 ug every IV boluses for postoperative pain relief, to be administrated every five minutes up to a maximum of 200 ug to keep VAS less than 4 until the patient regained his full conscious where he started usage of fentanyl patient controlled analgesia (PCA). Pain assessed by visual analogue score (0–10 scale, where 0 = no pain, and 10 = excruciating pain). The nurses evaluated the patients every five minutes or at the patient’s request. Patient transferred to renal transplant unit (RTU) for his hospital stay after fulfilling criteria for discharge, and endorsed to his primary nurse.

**Results**

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 50mcg in the average consumption of opioid in the recovery, assuming that the standard deviation of this variable is 54.4 according to Seveine etal, 2008. With significant level of 0.05, and a power of 0.9.

**Table (1) Body weight**

|  | Lidocaine group | 25 | 69.92 | ±12.052 | 0.601 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 67.44 | ±20.183 |  |

**Table (2) AGE**

|  | Lidocaine group | 25 | 38.80 | ±11.489 | 0.098 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 43.72 | ±8.970 |  |

Regarding age and body weight no significant changes within the two groups.

**Table (3) Preoperative heart rate**

|  | Drug  | N | Mean | Std. Deviation | Std. Error Mean |
| --- | --- | --- | --- | --- | --- |
|  | Lidocaine group | 25 | 82.32 | 6.908 | 0.032 |
| Fentanyl group | 25 | 86.28 | 5.675 |  |

Table (1) shows no difference in the preoperative heart rate.

**Table (4) preoperative mean blood pressure**

|  | Lidocaine group | 25 | 96.44 | ±6.777 | 0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 103.28 | ±6.478 |  |

Preoperative mean blood pressure measurement shows no statistical difference between the two groups.

**Table (5) Intraoperative heart rate (HR)**

|   | Lidocaine group | 25 | 61.92 | ±6.075 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 89.32 | ±5.907 |  |

Changes in the intraoperative heart rate shows significant difference between the two groups (P value <0.001).

**Table (6) intraoperative mean blood pressure**

|  | Lidocaine group | 25 | 74.28 | ±6.655 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 104.08 | ±7.182 |  |

There is a significant difference between the two groups regarding intraoperative mean arterial blood pressure with P value <0.001.

**Table (7) Heart rate in the recovery**

|  | Lidocaine group | 25 | 73.32 | ±7.169 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 111.12 | ±6.597 |  |

Regarding heart rate in the recovery there is a significant increase in the rate in the fentanyl group to the lidocaine group with P value <0.001.

**Table (8) Mean blood pressure changes in the recovery**

|  | Lidocaine group | 25 | 74.28 | ±6.655 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 107.64 | ±7.979 |  |

Regarding mean blood pressure in the recovery there is a significant increase in the mean blood pressure in the fentanyl group to the lidocaine group with P value <0.001.

**Table (9) Intraoperative MAC of sevoflurane**

|  | Lidocaine group | 25 | 1.700 | ±0.2500 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 2.640 | ±0.4899 |  |

There is significant changes between the two groups with increase consumption of sevoflurane in the fentanyl group. P value <0.001.

**Table (10) Visual Analogue Score (VAS) in the recovery**

|  | Lidocaine group | 25 | 2.64 | ±2.481 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 6.68 | ±1.345 |  |

There is an increase in the visual analogue score in fentanyl group to the lidocaine group showing significant difference with P value <0.001.

**Table (11) Consumption of opioid (fentanyl) in the recovery**

|  | Lidocaine group | 25 | 26.00 | ±43.87 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 116.96 | ±37.92 |  |

There is significant difference between the 2 groups with P value <0.001, increase opioid consumption in the form of fentanyl in the fentanyl group more than the lidocaine group.

**Table (12) First 24 hours demand of** **postoperative controlled analgesia (PCA)**

|  | Lidocaine group | 25 | 74.24 | ±40.882 | 0.235 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 61.00 | ±36.860 |  |

There is no significant difference between the 2 groups regarding first 24 hours demands of the PCA

**Table (13) postoperative controlled analgesia (PCA) doses given the first 24 hours**

|  | Lidocaine group | 25 | 36.76 | ±14.895 | 0.954 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 36.52 | ±14.336 |  |

This table shows no significant difference between the two groups regarding PCA doses given postoperative.

**Table (14) Time required for the first dose in the recovery**

|  | Lidocaine group | 25 | 45.88 | ±19.404 | <0.001 |
| --- | --- | --- | --- | --- | --- |
| Fentanyl group | 25 | 14.64 | ±4.281 |  |

Time required for the first analgesic dose shows shorter time on the fentanyl group (14.64 ±4.281) in comparison to the lidocaine group ( 45.88 ±19.404), with significant difference of P value<0.001.

***Discussion ( main paper)***

Intravenous lidocaine has been shown to be analgesic and anti-inflammatory medication with modulation of excessive inflammatory response. These properties are mediated by a variety of mechanisms, including sodium channel blockade,20 as well as inh1ibition of G protein–coupled receptors20,29 and N-methyl-D-aspartate receptors.30,31paper 2The 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.13paper 1 13 Pypendop BH, Ilkiw JE. The effects of intravenous lidocaine administration on the minimum alveolar concentration of isoflurane in cats. Anesth Analg 2005; 100: 97–101.

The possible anti-inflammatory mechanism for accelerating bowel function has been proposed, and more specifically lidocaine seems to target different steps within the inflammatory cascade, the increase in complement and pro-inflammatory cytokines. This requires a revision of the implementation of This includes several modalities aimed at minimizing the metabolic stress, enhancing the anti-inflammatory response and maximizing perioperative analgesia.

14,15 paper 1 14 Hollmann MW, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils. Anesthesiology 2001; 95: 113–22.

15 Herroeder S, Pecher S, Schonherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. Ann Surg 2007; 246: 192– 200.

The results of this study indicate that, in presence of low dose intraoperative opioid, and intravenous infusion of lidocaine 2% impacts on postoperative analgesia by decreasing the postoperative requirements of fentanyl in the recovery unit, the total opioid consumption in the recovery was found to provide a significant difference between the two groups where the fentanyl group consumed ( 116.9 ±37.92 ug of fentanyl) and the lidocaine group consumed ( 26.00 ± 43.87 ug of fentanyl) and these results corresponds to the result of paper 1 ( Severine etal,2008 and paper 3 ( BK Baral etal, 2010). No differences in self-reported pain scores were observed between the two groups within the first 24 hour after surgery, regarding PCA demand and supply no significant differences between the two groups.

The time required for the first analgesic in the recovery showed significant difference between the two groups, first analgesic dose in the fentanyl group was after (14.6 ± 4.281 minutes) in comparison to lidocaine group which took the first dose after ( 45.88 ± 19.404 minutes) this corresponds to the results of paper 3 (BK Baral etal, 2010) that compare the usage of lidocaine intraoperative to saline in decreasing postoperative pain killers as diclofenac to relief postoperative pain, patient received intraoperative lidocaine infusion prolonged the time required for the first analgesic dose.

Regarding inhalational gas requirements, lidocaine group showed decrease in consumption by 25% in comparison to the control group. This observation is in agreement with ( Severine etal,2008 and paper 3 ( BK Baral etal, 2010) which report a reduction in the concentration of inhalational agents with concurrent infusion of lidocaine but by different percentages than our study. According to paper 4 (Philip etal,2012) no changes between the two groups except with intubation.

Regarding hemodynamics, the lidocaine group showed more control with heart rate and mean blood pressure with less fluctuations than the fentanyl group which showed increase in postoperative heart rate and mean blood pressure due to pain and controlled by intravenous fentanyl postoperatively with significant difference of P value <0.001. the postoperative pain detected by pain numerical score, the aim of our study to keep numerical pain score less than 4. There was significant difference between with P value <0.001 between the two groups, the fentanyl group showed more pain than the lidocaine group.