1 Comparison of the Effect of Intraoperative 1 mg/kg/h and 2 mg/kg/h IV Lidocaine

2 Infusion on Postoperative Pain and Nausea-Vomiting in Laparoscopic Gastric

3

Bypass Surgery

- 4
- 5

6 **Objective**: To relieve postoperative pain and nausea and vomiting, various drugs and 7 methods, including intraoperative IV lidocaine infusion in different surgeries. However, the 8 exact same dose has not yet been determined. The purpose of this study was to evaluate and 9 compare the effect of intraoperative 1 mg/kg/h and 2 mg/kg/h IV lidocaine infusion on 10 postoperative pain and nausea-vomiting in laparoscopic gastric bypass surgery.

11 *Methods*: This clinical trial study was performed on patients undergoing laparoscopic 12 gastric bypass surgery in Rasoul-e-Akram Hospital, Iran. Patients were randomly assigned 13 into two groups (1 mg/kg/h lidocaine) and (2 mg/kg/h lidocaine). Postoperative pain and 14 nausea and vomiting were evaluated at times 0, 30 min, 1 h, 6 h, 12 h and 24 h after surgery. 15 Data was analyzed using statistical tests and SPSS 22.

16 **Results**: There was no significant difference in the effect of intraoperative 1 mg/kg/h and 2

17 mg/kg/h IV lidocaine infusion on static and dynamic pain and nausea-vomiting, agitation,

18 systolic BP, diastolic BP, pulse rate and postoperative administration of pethidine in 19 laparoscopic gastric bypass (P > 0.05).

20 **Conclusion**: Based on results of this study, administration of low dose lidocaine (1 mg/kg/h) 21 can be considered as an appropriate dose of IV lidocaine infusion in order to control

22 postoperative pain and nausea and vomiting in laparoscopic gastric bypass surgery.

23 Keywords: lidocaine, pain, nausea-vomiting, gastric bypass

24 **1. Introduction**

25 In post-operative time, it is important to control and reduce postoperative pain and nausea-26 vomiting (1). Different drugs and methods are used to relieve postoperative pain and nausea 27 and vomiting in different surgeries (2). One of these methods, which has been studied on 28 numerous occasions, is intraoperative intravenous (IV) lidocaine infusion undergone in a 29 wide range of surgical procedures such as laparotomy, laparoscopy, gynecological surgery, 30 orthopedics, etc., and has a positive effect in most cases in reducing postoperative pain and 31 nausea-vomiting (3). Considering the pharmacological effects of IV lidocaine, which has 32 both anti-inflammatory and anti-analgesic effects (protein receptor inhibitor G and NMDA), 33 lidocaine has been used to relieve postoperative pain (4). According to numerous studies on 34 various surgical procedures, intraoperative IV lidocaine infusion has been shown to reduce 35 postoperative pain and nausea and vomiting (5-14). Although the exact same dosage is still 36 unknown, the conducted studies have used 1-2 mg/kg/h dosages. In a double-blind clinical

37 trial on 41 patients undergoing microdistomy in two groups receiving 1.5 mg/kg/h lidocaine 38 infusion and normal saline infusion as placebo, Kim et al (2014) concluded that fentanyl 39 administration and postoperative pain intensity were significantly lower in the lidocaine 40 group except 48 hours after surgery. Total fentanyl administration, hospital stay and 41 satisfaction were significantly lower in lidocaine group than placebo group. Finally, 42 intraoperative systemic infusion of lidocaine reduces pain level during microdistomy surgery 43 (6). According to the studies, this study tends to evaluate and compare the effect of 44 intraoperative 1 mg/kg/h and 2 mg/kg/h IV lidocaine infusion on postoperative pain and 45 nausea-vomiting in laparoscopic gastric bypass to determine a more suitable and effective 46 dosage.

47 2. Materials and Methods

48 This study was a randomized clinical trial. The studied population included elective patients 49 who were candidate for laparoscopic gastric bypass referred to Rasoul-e-Akram Hospital 50 since June 2014 to March 2015. Sampling method was convenient sampling. Sample size was 51 determined using Cohen table with 80% statistical power, 0.05 alpha and 0.9 accuracy (21 52 subjects in each group). This study was a randomized clinical trial. Block randomization was 53 done in quadrilateral blocks. This study was performed on 42 elective patients who were 54 candidate for laparoscopic gastric bypass referred to Rasoul-e-Akram Hospital since June 55 2014 to March 2015. After obtaining consent and qualifying patients for inclusion and 56 exclusion, 41 patients were assigned into 2 groups of 21 patients (A and B) in 4 blocks. After 57 entering the operating room, standardized monitoring (ECG-POM-NIBP-Etco2) and insertion 58 of two 20G IV catheters and 3 cc/kg crystalloid serum infusion were performed for all 59 patients. Then, 3 mcg/kg fentaryl based on TBW and 0.02 mcg/kg midazolam based on TBW 60 were administered as premedication for all patients. For induction, all patients received 5 61 mg/kg thiopental sodium based on TBW followed by 0.2 mg/kg atracurium based on IBW 62 and 1.5 mcg/kg bolus lidocaine based on IBW for general anesthesia. After intubation of the 63 patients, all of them received 1.2 mac isoflurane followed by 0.03 mg/kg atracurium every 30 64 minutes and 50 mcg fentanyl every 40 minutes as maintenance. From the beginning of 65 surgery, group A received 1 mg/kg/h IV lidocaine infusion and group B received 2 mg/kg/h 66 IV lidocaine infusion by the pump until the end of surgery for a maximum of 4 hours. After 67 the end of surgery and discontinuation of all drugs, patients were placed in reserve by 0.0468 mg/kg nisosigine and 0.02 mg/kg atropine and extubation was done; patients were transferred

69 to PACU (recovery). The time to enter recovery was set at t=0; for 24 h, patients were 70 monitored for pain based on numerical rating score (0-10), static and dynamic nausea-71 vomiting, blood pressure (BP), heart rate and agitation in predicted times in the recovery or

52 surgery wards.

- 73 Finally, pain level was recorded in two A and B groups based on numerical rating score (0-
- 10) at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after surgery.
- 75 Pain level was recorded in two A and B groups based on numerical rating score (0-10) at
- times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after surgery. Static and dynamic nausea-vomiting
- was recorded in two A and B groups at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after surgery.
- Agitation was recorded in two A and B groups at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h
- after surgery. Systolic BP, diastolic BP and heart rate were recorded in 2 groups A and B at
- times 0, 30 min, and 1 h after surgery.
- 81 Finally, data was analyzed by SPSS software version 22. In the analytical step, Kolmogorov-
- 82 Sminov test was used for determining normality of quantitative values. Then, independent T-
- 83 test or Mann-Whitney U-test were used for comparing the quantitative variables of two
- 84 groups A and B. Chi-square test (Z) was used to compare the qualitative variables. Repeated
- 85 measure ANOVA or Friedman test was used to check and compare the changes.

86 **3. Results**

In this study, 42 patients who were referred to surgery ward of the Rasoul-e-Akram Hospital
in 2016 and underwent laparoscopic elective gastric bypass were enrolled in the study. In
group A, 21 patients (50%) received intraoperative 1 mg/kg/h IV lidocaine infusion; in group
B, 21 patients (50%) received intraoperative 2 mg/kg/h IV lidocaine infusion.

3.1. Determining and Comparing Pain in Two Groups A and B Based on Numerical Rating Score at Times 0, 30 min, 1 h, 6 h, 12 h and 24 h after Laparoscopic Gastric Bypass

In order to compare the pain level in 2 groups A and B based on numerical rating score at
times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after laparoscopic gastric bypass, the Mann-Whitney
U-test was used. Friedman test was used for comparison at times 0, 30 min, 1 h, 6 h, 12 h and
24 h after laparoscopic gastric bypass in each of the two groups A and B (separately).
Descriptive features and comparison of pain levels are summarized in Table 1.

98

Time	Group		Tost statistic	n value
	A (mean \pm SD)	B (mean \pm SD)	Test statistic	p-value
0	1.67 ± 1.01	1.71 ± 0.78	0.014	0.989
30 min	2.67 ± 0.73	2.67 ± 0.65	0.139	0.889
1 h	3.29 ± 0.84	3.19 ± 0.98	0.346	0.729
6 h	5.71 ± 0.9	5.57 ± 1.2	0.898	0.369
12 h	4.86 ± 0.96	4.71 ± 0.95	0.404	0.687
24 h	3.95 ± 1.39	3.81 ± 1.03	0.199	0.842

99
100Table 1: descriptive features and comparison of pain level in two groups A and B based on numerical rating score at
times 0, 30 min, 1 h, 6 h, 12 h and 24 h after laparoscopic gastric bypass

101 Based on the results of Table 1, there was no significant difference between pain levels of 102 patients in 2 groups A and B based on numerical rating score at times 0, 30 min, 1 h, 6 h, 12 103 h, and 24 h after laparoscopic gastric bypass (P>0.05). There was a significant difference 104 between pain levels of patients based on numerical rating score at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after laparoscopic gastric bypass in group A (P < 0.001, $X^2 = 94.18$). There was a 105 106 significant difference between pain levels of patients based on numerical rating score at times 107 0, 30 min, 1 h, 6 h, 12 h, and 24 h after laparoscopic gastric bypass in group B (P<0.001, 108 $X^2 = 88.29$).

3.2. Determining and Comparing Static Nausea-Vomiting in Two Groups A and B at Times 0, 30 min, 1 h, 6 h, 12 h and 24 h after Laparoscopic Gastric Bypass

In order to compare static nausea-vomiting levels in 2 groups A and B after laparoscopic gastric bypass, Z-test was used. Friedman test was used for comparison at times 0, 30 min, 1 h, 6 h, 12 h and 24 h after laparoscopic gastric bypass in each of the two groups A and B (separately). Frequency values and nausea-vomiting comparison are summarized in Table 2.

115 116

 Table 2: descriptive features and comparison of static nausea-vomiting levels in two groups A and B after laparoscopic gastric bypass

Time	Group		Test statistic	n valua
	A (N, %)	B (N, %))	Test statistic	p-value
0	2 (9.5%)	5 (23.8%)	1.26	0.896
30 min	4 (19%)	3 (14.3%)	0.4	0.655
1 h	0 (0%)	1 (4.8%)	0.22	0.587
6 h	0 (0%)	0 (0%)	0	0.5
12 h	0 (0%)	0 (0%)	0	0.5
24 h	0 (0%)	0 (0%)	0	0.5

Based on the results of Table 2, there was no significant difference between static nauseavomiting levels of patients in 2 groups A and B at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after laparoscopic gastric bypass (P>0.05). There was a significant difference between static nausea-vomiting levels of patients at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after laparoscopic gastric bypass in group A (P=0.01, $X^2=15$). There was a significant difference

- between static nausea-vomiting levels of patients at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h
- 123 after laparoscopic gastric bypass in group B (P=0.008, $X^2=15.73$).
- 124 3.3. Determining and Comparing Dynamic Nausea-Vomiting in Two Groups A and B at Times
- 125 0, 30 min, 1 h, 6 h, 12 h and 24 h after Laparoscopic Gastric Bypass
- 126 In order to compare dynamic nausea-vomiting levels in 2 groups A and B after laparoscopic
- 127 gastric bypass, Z-test was used. Friedman test was used for comparison at times 0, 30 min, 1
- 128 h, 6 h, 12 h and 24 h after laparoscopic gastric bypass in each of the two groups A and B
- 129 (separately). Frequency values and nausea-vomiting comparison are summarized in Table 3.
- 130 131

 Table 3: descriptive features and comparison of dynamic nausea-vomiting levels in two groups A and B after

 laparoscopic gastric bypass

Time	Group		Test statistic	n valua
	A (N, %)	B (N, %))	i est statistic	p-value
0	8 (38.1%)	6 (28.6%)	0.65	0.742
30 min	14 (66.7%)	11 (52.4%)	0.95	0.828
1 h	5 (23.8%)	5 (23.8%)	0	0.5
6 h	0 (0%)	0 (0%)	0	0.5
12 h	0 (0%)	0 (0%)	0	0.5
24 h	0 (0%)	0 (0%)	0	0.5

Based on the results of Table 3, there was no significant difference between dynamic nausea-

vomiting levels of patients in 2 groups A and B at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h

134 after laparoscopic gastric bypass (P>0.05). There was a significant difference between

- dynamic nausea-vomiting levels of patients at times 0, 30 min, 1 h, 6 h, 12 h, and 24 h after
- 136 laparoscopic gastric bypass in group A (P=0.001, $X^2=45$). There was a significant difference
- between dynamic nausea-vomiting levels of patients at times 0, 30 min, 1 h, 6 h, 12 h, and 24
- h after laparoscopic gastric bypass in group B (P=0.001, X²=33.77).

3.4. Determining and Comparing Agitation in Two Groups A and B at Times 0, 30 min and 1 h after Surgery

In order to compare agitation levels in 2 groups A and B after laparoscopic gastric bypass, Ztest was used. Friedman test was used for comparison at times 0, 30 min and 1 h after surgery in each of the two groups A and B (separately). Frequency values and agitation comparison

- are summarized in Table 4.
- 145
146Table 4: descriptive features and comparison of agitation levels in two groups A and B after laparoscopic gastric
bypass

Time	Group		Tost statistia	n valua
	A (N, %)	B (N, %))	Test statistic	p-value
0	6 (28.6%)	5 (23.8%)	0.35	0.636
30 min	5 (23.8%)	6 (28.6%)	0.35	0.636
1 h	1 (4.8%)	1 (4.8%)	0	0.5

Based on the results of Table 4, there was no significant difference between agitation levels

- of patients in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass
- 149 (P>0.05). There was no significant difference between agitation levels of patients at times 0,
- 150 30 min and 1 h after laparoscopic gastric bypass in group A (P=0.072, X^2 =5.25). There was
- 151 no significant difference between agitation levels of patients at times 0, 30 min and 1 h after
- 152 laparoscopic gastric bypass in group B (P=0.097, X²=4.66).

153 **3.5.** Determining and Comparing Systolic BP in Two Groups A and B at Times 0, 30 min and 1

154 h after Laparoscopic Gastric Bypass

In order to compare systolic BP levels in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass, independent t-test and Mann-Whitney U-test were used. Friedman test and repeated measure test were used for comparison of systolic BP levels at times 0, 30 min and 1 h after laparoscopic gastric bypass in each of the two groups A and B (separately). Descriptive features and comparison of systolic BP are summarized in Table 5.

160
161Table 5: descriptive features and comparison of systolic BP levels in two groups A and B at times 0, 30 min and 1 h
after laparoscopic gastric bypass

Time	Group		Tost statistic	n volue
	A (mean \pm SD)	$B (mean \pm SD)$	Test statistic	p-value
0	141.76 ± 13.68	141.9 ± 14.92	0.032	0.974
30 min	139.33 ± 13.13	139.43 ± 15.27	0.025	0.98
1 h	134.05 ± 11.38	136.48 ± 10.42	0.768	0.477

Based on the results of Table 5, there was no significant difference between systolic BP levels of patients in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass (P>0.05). There was a significant difference between systolic BP levels of patients at times 0, 30 min and 1 h after laparoscopic gastric bypass in group A (P<0.001, $X^2=27.71$). There was a significant difference between systolic BP levels of patients at times 0, 30 min and 1 h after laparoscopic gastric bypass in group B (P=0.012, $X^2=5.59$).

3.6. Determining and Comparing Diastolic BP in Two Groups A and B at Times 0, 30 min and 1 h after Laparoscopic Gastric Bypass

In order to compare diastolic BP levels in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass, independent t-test was used. Repeated measure test was used for comparison of diastolic BP levels at times 0, 30 min and 1 h after laparoscopic gastric bypass in each of the two groups A and B (separately). Descriptive features and comparison of diastolic BP are summarized in Table 6.

Time	Group		Tost statistia	n valua
Time	A (mean \pm SD)	B (mean \pm SD)	Test statistic	p-value
0	91.24 ± 8.24	93.05 ± 9.71	0.651	0.519
30 min	89.57 ± 9.3	91.19 ± 11.27	0.508	0.615
1 h	86.24 ± 9.54	89.14 ± 7.35	1.18	0.245

175
176Table 6: descriptive features and comparison of diastolic BP levels in two groups A and B at times 0, 30 min and 1 h
after laparoscopic gastric bypass

Based on the results of Table 6, there was no significant difference between diastolic BP levels of patients in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass (P>0.05). There was a significant difference between diastolic BP levels of patients at times 0, 30 min and 1 h after laparoscopic gastric bypass in group A (P<0.001, X^2 =58.94). There was a significant difference between diastolic BP levels of patients at times 0, 30 min

and 1 h after laparoscopic gastric bypass in group B (P=0.001, X²=11.38).

183 3.7. Determining and Comparing Heart Rate in Two Groups A and B at Times 0, 30 min and 1 184 h after Laparoscopic Gastric Bypass

In order to compare heart rate in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass, independent t-test and Mann-Whitney test were used. Repeated measure test and Friedman test were used for comparison of heart rate at times 0, 30 min and 1 h after laparoscopic gastric bypass in each of the two groups A and B (separately). Descriptive features and comparison of heart rate are summarized in Table 7.

190 191

 Table 7: descriptive features and comparison of heart rate in two groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass

Time	Group		Test statistic	n valua
	A (mean \pm SD)	B (mean \pm SD)	Test statistic	p-value
0	93.05 ± 7.32	96.86 ± 6.64	1.76	0.085
30 min	90.29 ± 6.66	92.86 ± 8.31	1.26	0.207
1 h	86.43 ± 6.47	88 ± 7.44	0.9	0.364

Based on the results of Table 7, there was no significant difference between heart rate of patients in 2 groups A and B at times 0, 30 min and 1 h after laparoscopic gastric bypass (P>0.05). There was a significant difference between heart rate of patients at times 0, 30 min and 1 h after laparoscopic gastric bypass in group A (P<0.001, X^2 =28.5). There was a significant difference between heart rate of patients at times 0, 30 min and 1 h after laparoscopic gastric bypass in group B (P=0.001, X^2 =67.43).

3.8. Determining and Comparing the First, Second and Third Pethidine Administrations in Two Groups A and B after Laparoscopic Gastric Bypass

In order to compare the first, second and third pethidine administrations in 2 groups A and B after laparoscopic gastric bypass, Z-test was used. Frequency values and comparison of the first, second and third pethidine administrations in groups A and B after laparoscopic gastric bypass are summarized in Table 8.

204
205Table 8: descriptive features and comparison of the first, second and third pethidine administrations in two groups A
and B after laparoscopic gastric bypass

Time	Group		Tost statistic	n volue
	A (N, %)	B (N, %)	Test statistic p	p-value
1 st	6 (28.6%)	11 (52.3%)	1.61	0.053
2 nd	12 (57.1%)	8 (38%)	1.26	0.103
3 rd	3 (14.3%)	1 (4.8%)	1.06	0.144

Based on the results of Table 8, there was no significant difference between the first, second
and third pethidine administrations in 2 groups A and B after laparoscopic gastric bypass
(P>0.05).

209 **4. Discussion**

210 According to the most important results of this study, there was no significant difference 211 between the effect of intraoperative 1 mg/kg/h and 2 mg/kg/h IV lidocaine infusion on 212 postoperative pain, static and dynamic nausea-vomiting, agitation, systolic BP, diastolic BP, 213 heart rate and pethidine administration after laparoscopic gastric bypass. In both groups, 214 intraoperative 1 mg/kg/h and 2 mg/kg/h IV lidocaine infusion significantly increased pain 6 215 hours postoperatively and significantly decreased pain 24 hours postoperatively. Moreover, 216 postoperative static and dynamic nausea-vomiting, agitation, systolic BP, diastolic BP and 217 heart rate significantly decreased 0-24 hours after the surgery. Therefore, lidocaine seems to 218 reduce postoperative pain and complications. However, high-dose and low-dose lidocaine has 219 the same significant effect in reducing pain and complications after laparoscopic gastric 220 bypass.

Postoperative pain not only causes physical and mental torment, but also increases the risk of side effects and delayed recovery. Therefore, it is important to eliminate emotional pain and stress to maintain comfortable recovery, reduce the incidence of postoperative cardiovascular complications and increase sooner discharge (15). It has been previously reported that preoperative IV lidocaine infusion can increase postoperative analgesic effects and accelerate early recovery; intraoperative continuous infusion can effectively prevent central hyperalergy 227 through the pain pathway (16). Lidocaine has an insignificant opioid-sparing property in 228 patients undergoing various surgical procedures (17, 18). Several mechanisms have been 229 suggested to explain the insignificant opioid-sparing effect of preoperative lidocaine. First, 230 lidocaine has anti-inflammatory properties which can minimize the pain caused by surgical 231 inflammation (19, 20). Second, lidocaine also can directly block the pathways of pain 232 conducting sodium channels (21). Eventually, lidocaine can reduce the need for opioid drugs 233 or intraoperative volatile anesthetics, which may reduce the progression of postoperative pain 234 (22, 24).

235 Based on literature review, this study was the first study to compare the effects of two 236 different doses of lidocaine (1 mg/kg/h vs. 2 mg/kg/h IV infusion) on postoperative pain and 237 nausea-vomiting after laparoscopic gastric bypass. However, many studies have shown that 238 different doses of lidocaine infusion reduced postoperative pain level and side effects, 239 compared with placebo and other drugs. For example, Tikuišis et al (2014) studied 64 240 patients undergoing laparoscopic colon surgery and found that pain level significantly 241 decreased 24 h after the surgery in both rest and movement in 2 mg/kg/h lidocaine group 242 compared to placebo group. Moreover, there was no significant difference between 243 postoperative complications between the two groups (5). Through a meta-analysis, Ventham 244 et al. (2015) reviewed 40 clinical trials on comparing the effect of lidocaine infusion with 245 placebo or routine postoperative laparoscopic treatments and found that lidocaine 246 intervention reduced the pain score at rest in 2, 12 and 24 hours after surgery and reduced 247 nausea and vomiting (9). ... et al (2015) studied 226 patients undergoing laparoscopic 248 gynecological surgery and revealed that 1% lidocaine infusion was more effective on 249 postoperative pain than placebo (12). Terkawi et al (2016) found no significant difference in 250 pain scores between the two groups by follow-up of 216 patients after 2 days of abdominal 251 surgery in two groups of 1 mg/kg/h IV Lidocaine infusion and epidural analgesia. In 252 lidocaine group, episodes of hypotension and postoperative nausea and vomiting were less 253 frequent than placebo group (14).

In the above studies, pain and nausea-vomiting were not compared between two groups of 1 mg/kg/h and 2 mg/kg/h lidocaine; positive effect of lidocaine in reducing pain and nauseavomiting in most of these studies may be due to the fact that lidocaine has been compared with opiate and placebo. Moreover, inconsistency of this study with some studies may be due to differences in samples, design of studies, lidocaine doses and surgical site and procedures. In the present study in which patients were carefully monitored for up to 24 hours after surgery, although administration of high-dose lidocaine did not cause side effects after

261 surgery, administration of low doses, as high doses, reduced pain, nausea-vomiting and

- agitation. Therefore, low doses of lidocaine (1 mg/kg/h), rather than high doses (2 mg/kg/h),
- 263 can be used as an appropriate dose of IV lidocaine infusion to control postoperative pain and
- 264 nausea-vomiting in laparoscopic gastric bypass.

265 **5. Conclusion**

Based on the results of this study, low doses of lidocaine (1 mg/kg/h), rather than high doses (2 mg/kg/h), can be used as an appropriate dose of IV lidocaine infusion to control postoperative pain and nausea-vomiting in laparoscopic gastric bypass.

269

270 References

- 1. Christopher L. Wu. Acute Postoperative Pain. In: Miller RD, ed. Miller's Anesthesia, 6thed.
- 273 Philadelphia; Churchill Livingstone, 2005; 2729- 2750.
- 2. McCracken G, Houston P, Lefebvre G.Guideline for the Management of Postoperative
 Nausea and Vomiting. JULY JOGC JUILLET ;2008July No. 209.
- 3. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on
 postoperative analgesia and recovery from surgery: a systematic review of randomized
 controlled trials. Drugs. 2010 Jun 18;70(9):1149-63.
- 4. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M,
- 280 Steegers MA, et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on
- the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2015 Dec 18.
- 5. Tikuišis R , Miliauskas P, Samalavičius NE, Žurauskas A, Samalavičius R, Zabulis V.
 Intravenous lidocaine for post-operative pain relief after hand-assisted laparoscopic colon
 surgery: a randomized, placebo-controlled clinical trial. Tech Coloproctol. 2014
 Apr;18(4):373-80.
- 286 6. Kim KT, Cho DC, Sung JK, Kim YB, Kang H, Song KS, Choi GJ. Intraoperative systemic
- 287 infusion of lidocaine reduces postoperative pain after lumbar surgery: a double-blinded,
- randomized, placebo-controlled clinical trial. Spine J 2014; 14:1559 –1566.
- 289 7. Patrick Tauzin-Fin, Olivier Bernard, Musa Sesay, Matthieu Biais, Philippe Richebe, Alice
 290 Quinart, et al. Benefits of intravenous lidocaine on post-operative pain and acute
 291 rehabilitation

- after laparoscopic nephrectomy. J Anaesthesiol Clin Pharmacol. 2014 Jul-Sep; 30(3): 366–
 372.
- 294 8. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, et al.
- 295 Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery.
- 296 Cochrane Database Syst Rev. 2015 Jul 16;7:CD009642
- 297 9. Ventham NT, Kennedy ED, Brady RR, Paterson HM, Speake D, Foo I, Fearon KC.
- 298 Efficacy of Intravenous Lidocaine for Postoperative Analgesia Following Laparoscopic
- 299 Surgery: A Meta-Analysis. World J Surg. 2015 Sep;39(9):2220-34.
- 300 10. Ahn E, Kang H, Choi GJ, Park YH, Yang SY, Kim BG, et al. Intravenous lidocaine for
- 301 effective pain relief after a laparoscopic colectomy: a prospective, randomized, double-blind,
- 302 placebocontrolled study. Int Surg. 2015 Mar;100(3):394-401.
- 303 11. Hesham F. Solimana, Ahmed R. Gharbiya . Efficacy of systemic lidocaine infusion
- 304 compared with systemic ketorolac infusion in improvement of recovery after laparoscopic
- bariatric surgery. Ain-Shams Journal of Anesthesiology. 2015; 8: 334-40.
- 306 12. Selcuk S, Api M, Polat M, Arinkan A , Aksoy B, Akca T, et al. Effectiveness of local
- 307 anesthetic on postoperative pain in different levels of laparoscopic gynecological surgery.
- 308 Arch Gynecol Obstet. 2015 Dec 15. [Epub ahead of print]
- 309 13. Yang W, Hu WL. Effects of intravenously infused lidocaine on analgesia and
- 310 gastrointestinal function of patients receiving laparoscopic common bile duct exploration.
- 311 Pak J Med Sci. 2015 Sep-Oct;31(5):1073-7.
- 312 14. Terkawi AS, Tsang S, Kazemi A, Morton S, Luo R, Sanders DT, et al. A Clinical
- 313 Comparison of Intravenous and Epidural Local Anesthetic for Major Abdominal Surgery.
- 314 Reg Anesth Pain Med. 2016 Jan-Feb;41(1):28-36.
- 315 15.Hui V, Hyman N, Viscomi C, Osler T. Implementing a fasttrack protocol for patients
- undergoing bowel resection: not so fast. Am J Surg. 2013;206(2):152-158.
- 317 16. Gil V, Parsons S, Gallego D, Huizinga J, Jimenez M. Effects of hydrogen sulphide on
- 318 motility patterns in the rat colon. Br J Pharmacol. 2013;169(1):34-50.
- 319
- 17. De Oliveira GS Jr, Duncan K, Fitzgerald P, Nader A, Gould RW, McCarthy RJ. Systemic
 lidocaine to improve quality of recovery after laparoscopic bariatric surgery: a randomized
- double-blinded placebocontrolled trial. Obes Surg 2014; 24:21 2–218.
- 323 18. Vigneault L, Turgeon AF, Cöté D, Lauzier F, Zarychanski R, Moore L, et al.
- 324 Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of
- randomized controlled trials. Can J Anaesth 2011; 58: 22–37.

- 326 19. Jeong HJ, Lin D, Li L, Zuo Z. Delayed treatment with lidocaine reduces mouse microglial
- 327 cell injury and cytokine production after stimulation with lipopolysaccharide and interferon γ .
- 328 Anesth Analg 2012; 114:856–861.
- 329 20. Suto T, Obata H, Tobe M, Oku H, Yokoo H, Nakazato Y. Longterm effect of epidural
- 330 injection with sustained-release lidocaine particles in a rat model of postoperative pain. Br J
- 331 Anaesth 2012;109:95 7–967.
- 332 21. Obreja O, Hirth M, Turnquist B, Rukwied R, Ringkamp M, Schmelz M. The differential
- 333 effects of two sodium channel modulators on the conductive properties of C-fi bers in pig
- 334 skin in vivo. Anesth Analg 2012; 115:56 0–571.
- 335 22. Hamp T, Krammel M, Weber U, Schmid R, Graf A, Plöchl W. The effect of a bolus dose
- 336 of intravenous lidocaine on the minimum alveolar concentration of sevofl urane: a
- 337 prospective, randomized, double-blinded, placebo-controlled trial. Anesth Analg 2013;
- 338 117:32 3–328.
- 339 23. Cho AR, Kwon JY, Kim KH, Lee HJ, Kim HK, Kim ES, et al. The effects of anesthetics
- on chronic pain after breast cancer surgery. Anesth Analg 2013; 116:68 5–693.
- 341 24. Petrenko AB, Ishii H, Kohno T, Baba H. When similar is not alike: decreased sensory
- 342 thresholds after intravenous infusion of remifentanil may not be remifentanil-induced
- 343 hyperalgesia. Anesth Analg 2012; 11 5:977.