

١ **Intraperitoneal Instillation of Lidocaine for Postoperative Pain Relief after**
٢ **Total Abdominal Hysterectomy: a Double Blinded Randomized Placebo-**
٣ **controlled Trial**

٤ Ziba Zahiri Sorouri^a,Forozan Milani^{b*}, Abtin Heidarzadeh^b, Masoumeh Akhavan Azaria
٥
٦

٧ ^aReproductive Health Research Center, Obstetrics and Gynecology Department, Alzahra
٨ Hospital, Guilan University of Medical Sciences, Rasht, Iran.^bVice chancellorship of Guilan
٩ University of Medical Sciences, Rasht, Iran

١٠
١١ **Corresponding author:** forozanmilani@yahoo.com
١٢

١٣ *Running title: Intraperitoneal instillation of lidocaine for postoperative pain relief .*

١٤

١٥

١٦

١٧

Abstract

١٨ Pain after total abdominal hysterectomy (TAH) is a major concern. Pain management is very important
١٩ issue after TAH. This study aimed to assess the efficacy of intraperitoneal instillation of lidocaine for
٢٠ postoperative pain relief after TAH. A double-blinded randomized placebo-controlled trial was conducted
٢١ on patients undergoing total abdominal hysterectomy in Al-zahra hospital from June 2007 to July 2008.
٢٢ Forty patients were randomly assigned with equal number in two lidocaine (N = 20) and normal saline (N
٢٣ = 20) groups. The lidocaine group received 50 mL of 0.8% lidocaine with epinephrine and placebo group
٢٤ received 50 ml of saline 0.9%. We used 10 cm visual analog scale (VAS) for assessing pain at 8, 12, and
٢٥ 24 h at rest and 48 h on movement. Opioid consumption, patient' satisfaction with pain control, and
٢٦ incidence of postoperative nausea and vomiting were assessed. Means of pain score at different times in
٢٧ lidocaine group were significantly lower than placebo group ($P < 0.05$) the difference between mean dose
٢٨ of opioid consumption over 24 h between two groups was not significant ($P = 0.785$). Patient's
٢٩ satisfaction score in lidocaine group was significantly higher than saline group ($P = 0.034$). Differences in
٣٠ incidence of postoperative nausea and vomiting between two groups were not significant ($P = 1.0$).
٣١ Intraperitoneal instillation of 50 mL of 0.8% lidocaine with epinephrine is an effective and safe technique
٣٢ for postoperative pain management after TAH. But this technique cannot reduce opioid consumption over
٣٣ 24 h after TAH.

٣٤ **Keywords:** Hysterectomy; Pain, Lidocaine; Intraperitoneal.

٣٥

٣٦

٣٧

Introduction

Abdominal hysterectomy is a prevalent surgery in women and causes extensive tissue injury. Pain after total abdominal hysterectomy (TAH) is a major concern and induces physical and psychological complications that can increase the length of the hospitalization (1, 2). Pain is usually classified into two main categories by the type of damage that causes it. These two categories are nociceptive and neuropathic pains. During surgery, tissue injury causes nociceptive pain and nerve damage causes neuropathic pain (1). Postoperative pain relief is very important issue in any surgery. The common postoperative pain management is traditionally based on opioids (4, 5). Considering opioids' adverse effects such as nausea, vomiting, sedation, drowsiness, and urinary retention (6, 7), recently there is a lot of interest for finding a safe and effective pain treatment after operation. Several new methods are introduced for postoperative pain relief (5). But there is not enough evidence about clinically impact of these techniques (8). Postoperative pain relief provides patient comfort and allows the patient to breathe, cough and move sooner. Also, it can reduce the incidence of complications after surgery (5, 9, and 10). Local anesthetics are recognized as a useful technique for postoperative pain management. They can reduce inflammatory response after surgery and produce analgesia by blocking neural transmission at the site of tissue injury (9). A suitable local anesthetic should be effective, safe, and inexpensive. Lidocaine is a proper and the most widely used local anesthetic. Lidocaine is used in several ways for managing the postoperative pain. Clinical studies that examine efficacy of lidocaine for postoperative pain relief, reported mixed results. Reduction in postoperative pain and opioids consumption are shown in several studies (10-16), whereas some studies failed to demonstrate beneficial effects (17-20). In this study we aimed to assess the efficacy of intraperitoneal instillation of lidocaine for postoperative pain relief after TAH.

Experimental

٦١

٦٢ *Materials and methods*

٦٣ *Trial design and setting*

٦٤ A two-arm parallel double-blinded randomized placebo-controlled trial with equal randomization
٦٥ (1:1) was conducted on patients undergoing total abdominal hysterectomy in Al-zahra hospital
٦٦ from June 2007 to July 2008. This hospital is the only governmental maternity hospital in Rasht
٦٧ in Guilan province, north of in Iran.

٦٨ *Patients*

٦٩ Eligible patients were all women who were undergoing total abdominal hysterectomy. Patients
٧٠ were excluded if they had history of hepatic, cardiovascular diseases, asthma, seizure disorder,
٧١ cancer, chronic pain, opioid addiction, hypersensitivity or allergy to local anesthetics, or require
٧٢ further surgeries.

٧٣ This study was approved by the Ethical Committee of Guilan University of Medical Sciences.

٧٤ All patients provided written informed consent before inclusion in the study.

٧٥ *Randomization and Interventions*

٧٦ A co-worker assigned participants to lidocaine and placebo groups using a random sequence that
٧٧ was prepared by a statistician with no clinical involvement in the trial. The randomization list
٧٨ was generated using permuted block size of four. Sealed envelopes labeled A or B were
٧٩ provided. After assignment, one of them was delivered to operating room. We put in each
٨٠ envelope one Syringe containing lidocaine or normal saline. Syringe for the lidocaine group
٨١ containing 50 mL of 0.8% lidocaine with epinephrine (1:500000 dilution, prepared by adding 30
٨٢ mL of normal saline to 20 mL of 2% lidocaine containing epinephrine 1:200000) and in the
٨٣ placebo group syringe containing 50 mL of normal saline 0.9%. All patients received a

standardized general anesthesia were induced with intravenous injection of sodium thiopental 4 mg/Kg, fentanyl 2 µg/Kg and neuromuscular blockade by 0.5 mg/Kg atracurium. Tracheal tube was inserted and anesthesia was maintained by isoflurane, nitrous oxide and oxygen. Atracurium was repeated as necessary. The hysterectomy was performed using standard technique; Surgery in all patients was performed via a standard Pfannenstiel incision after closure of vaginal cuff and visceral peritoneal, content of syringes was administered into the peritoneal cavity. At the end of surgery, neuromuscular blockade was reversed by administration of atropine 0.02 mg/Kg and neostigmine 0.04 mg/kg and the patients were extubated. In this trial, patients, research personnel, outcome assessor, and ward nursing staff were blind of group allocation.

Data collection and outcomes

Primary outcome of this trial was pain scores at 8, 12, and 24 h at rest and 48 h on movement (induced by sitting). We used 10 cm visual analog scale (VAS) (0 = no pain; 10 = worst pain) for assessing pain. Before surgery all participants were educated about use of VAS. Also we collected data about duration of surgery, Opioid consumption over 24 h after surgery, and incidence of postoperative nausea and vomiting. Also patients' satisfaction with pain control was assessed by interviewing at 24 h after surgery using a scale of 1 = poor, 2 = moderate, and 3 = good. Preoperative data including age, body mass index (BMI), and history of abdominal surgery were obtained by nurses that were not clinically involved in the trial.

Sample size

To detect a difference in 0.9 cm in pain score between two groups with an error probability of 5% and a power of 80%, assuming a standard deviation (SD) of 1 cm, a sample size of 20 patients per group was needed.

Statistical analysis

107 Data were analyzed in IBM SPSS Software Version 21. Descriptive and analytic statistics were
108 used. Numeric data were shown as mean and SD and categorical variables data were shown as
109 number and percentage. For statistical analysis, the non-parametric Mann Whitney U test was
110 used to compare pain scores in different postoperative times and satisfaction scores between two
111 groups. Two-tailed independent t-test was used to compare mean dose of opioid consumption,
112 duration of surgery, and age between two groups. Also Fisher's exact tests were used to compare
113 proportions between two groups. A P-value less than 0.05 has been considered as statistically
114 significant.

115

116

117

Results

118

119 During the period of study 51 patients underwent total abdominal hysterectomy were assessed
120 for eligibility. Forty patients were randomly assigned with equal number in two lidocaine (N =
121 20) and normal saline (N = 20) groups. All participants completed the trial (Figure 1). Baseline
122 characteristics of the participants in two groups are shown in Table 1.

123 Mean of duration of surgery in lidocaine group was 63 ± 13.41 min and in saline group was $66 \pm$
124 18.47 min that this difference was not significant ($P = 0.560$). Mean dose of pethidine
125 consumption over 24 h after surgery in lidocaine group was 106.25 ± 29.10 mg and saline group
126 was 108.75 ± 28.42 mg that this difference between two groups was not significant ($P = 0.785$).

127 Means of pain score at different time in lidocaine group were significantly lower than normal
128 saline group ($P < 0.05$) (Table 2, Figure 2). In lidocaine group 9 patients (45%) and in normal

129 saline group 3 patients (15%) defined their satisfactions as good. Mean of patient's satisfaction
130 score in lidocaine group was 2.20 ± 0.61 and in normal saline group was 1.5 ± 0.51 that this
131 difference between two groups was statistically significant ($P = 0.034$). Five patients (25%) in
132 lidocaine group and 5 patients (25%) in normal saline group experienced nausea, also vomiting
133 by 4 (20%) in lidocaine group and 5 (25%) in saline group was experienced, that these
134 differences between two groups were not significant ($P = 1.0$, $P = 1.0$).

135

136

137

138

Discussion

139 Lidocaine is the most widely used local anesthetic. Lidocaine like other sodium channel blockers
140 reduces pain by neural impulses blocking (21). To prolong the postoperative pain relief effect of
141 lidocaine, and reducing hepatic exposure and the risk of systemic reaction, lidocaine is usually
142 administrated in combination with vasoconstrictor such as epinephrine (15, 22).

143 The results of this study demonstrate that administration of intraperitoneal lidocaine with
144 epinephrine during TAH can significantly reduce postoperative pain at 8, 12, and 24 h at rest and
145 48 h on movement compared with normal saline. Also patients in lidocaine group were
146 significantly more satisfied with pain control than normal saline group. But this technique cannot
147 reduce pethidine consumption over 24 h after TAH. The incidence of nausea and vomiting in
148 both groups was similar.

149 Consistent with our findings in Williamson *et al.* study that examined intraperitoneal lignocaine
150 instillation for pain control after TAH, pain score at 24 h at rest was lower in lignocaine group
151 compared with saline significantly. Also there was no significant difference in morphine
152 consumption between two groups. But in contrast with our finding there was no significant
153 difference in pain score at 48 h on movement between two groups (15). Difference between our
154 finding and this study in 48 h on movement may be due to the concentration of lidocaine, we
155 used 50 mL of 0.8% lidocaine but in Williamson et al study 50 mL of 0.4% lidocaine was used.
156 In other randomized controlled trial, women who received preemptive analgesia with 20 mL of
157 1% lidocaine at the abdominal incision site prior to the performance of the hysterectomy
158 compared with saline, perceived lower pain at 2, 5 and 8 h significantly (14). Other study that
159 examined efficacy of intraperitoneal lidocaine instillation for post cesarean pain relief showed
160 that pain scores in women who received lidocaine were significantly lower on the first
161 postoperative day (23). Abdelazim *et al.* in a study that was carried out on patients who were
162 undergoing gynecological laparoscopy found that Intraperitoneal lidocaine can significantly
163 reduce pain and opioid consumption over 24 h after surgery compared with saline (16). Some
164 studies demonstrated efficacy of Intraperitoneal instillation of lidocaine for pain relief after
165 gynecological surgeries (11, 12, 22, 24 and 25). Also studies conducted on patients who were
166 undergoing other abdominal surgeries, demonstrated efficacy of intraperitoneal lidocaine for
167 reducing pain after surgery (13, 26 and 27). A systematic review identified intraperitoneal
168 instillation of local anesthetics during gynecologic laparoscopy significantly decreased pain
169 during a 6 h interval after operation but had no effect at 24 h after that (28). TAH causes
170 extensive tissue injury. Lidocaine is more effective in surgeries that cause more tissue injury
171 because provoke a greater inflammatory response (30), also the rate of absorption of lidocaine is

172 slower after hysterectomy than gynecological laparoscopy (15). Other systematic review
173 including eight randomized trials in gastrointestinal and gynecological surgery intraperitoneal
174 local anesthetic consistent with our findings reduced postoperative pain but not opioid
175 consumption (29).

176 **Conclusion**

177 In conclusion, intraperitoneal instillation of 50 mL of 0.8% lidocaine with epinephrine is an
178 effective and safe technique for postoperative pain relief over 24 h at rest and at 48 h on
179 movement after TAH. But this technique cannot reduce opioid consumption over 24 h after
180 TAH.

181 Further studies that assess pain in shorter time after operation and narrow interval among pain
182 assessment time and assess opioid consumption in each time is recommended.

183 **Acknowledgment**

184 This study was based on a thesis submitted by the third author to the Guilan University of
185 Medical Sciences in Iran. Thanks to the Vice Chancellor of Research of Guilan University of
186 Medical Sciences for funding this project. The authors sincerely thank Mr. Davoud Pourmarzi
187 for his help to edit manuscript. We sincerely appreciate the patients that participate in this
188 project.

189 **Author's Contribution:** Dr. ZibaZahiriSorouri; design, data collection and writing the man-
190 uscript. Dr. Forozan Milani and Masoumeh Akhavan Azari; data collection. Dr. Abtin
191 Heidarzadeh; statistical analysis.

۱۹۲

۱۹۳

۱۹۴

۱۹۵

۱۹۶

۱۹۷

۱۹۸

لطفا شماره رفرنس ها در داخل پرانتز قرار گیرد.

۱۹۹

۲۰۰

References

۲۰۱ 1-Brandsborg B.Pain following hysterectomy: epidemiological and clinical aspects.*Dan. Med.*

۲۰۲ *J.*(2012) 59:4374.

۲۰۳ 2- Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallumRCandGlaser R.

۲۰۴ Psychological influences on surgical recovery.Perspectives from psychoneuroimmunology.*Am.*

۲۰۵ *Psychol.*(1998) 53:1209- 1218.

۲۰۶ 3-Kelly DJ, Ahmad MandBrullSJ.Preemptive analgesia I: physiological pathways and

۲۰۷ pharmacological modalities. *Can. J.Anaesth.*(2001) 48:1000- 1010.

۲۰۸ 4- TordaTA .Postoperative analgesia.*Aust.Prescr.* (1995) 18:88-91.

۲۰۹ 5. Kehlet HandHolte K. Effect of postoperative analgesia on surgicaloutcome. *Br. J.Anaesth.*

۲۱۰ (2001)87:62–72.

۲۱۱ 6. Stanley G, Appadu B, Mead MandRowbotham DJ. Dose requirements, efficacy and side

۲۱۲ effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological

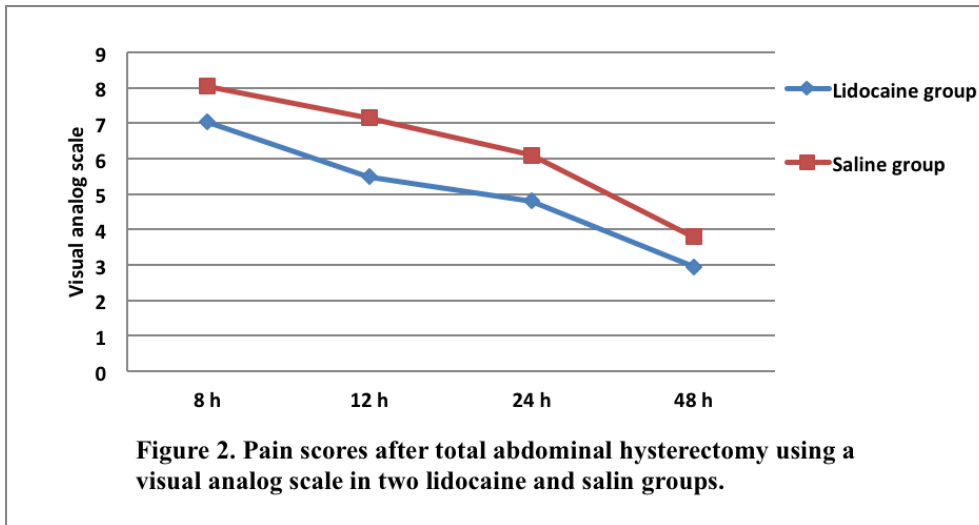
۲۱۳ surgery. *Br. J.Anaesth.* (1996)76:484–486.

- ๒๑๔ 7. Woodhouse A and Mather LE. The effect of duration of dose delivery with patient-controlled
 ๒๑๕ analgesia on the incidence of nausea and vomiting after hysterectomy.*Br.*
 ๒๑๖ *J.Clin.Pharmacol.*(1998)45:57–62.
- ๒๑๗ 8. Liu SS and Wu CL. Effect of postoperative analgesia on major postoperative complications: a
 ๒๑๘ systematic update of the evidence. *Anesth.Analg.*(2007)104: 689-702.
- ๒๑๙ 9. Antje B, Jürgen W, Harkirat C, Marcel E D and Gary S. Preventive Analgesia by Local
 ๒๒๐ Anesthetics: The Reduction of Postoperative Pain by Peripheral Nerve Blocks and Intravenous
 ๒๒๑ Drugs. *Anesth.Analg.*(2013) 116: 1141-61.
- ๒๒๒ 10. Marret E, Rolin M, Beaussier M and Bonnet F. Meta-analysis of intravenous lidocaine and
 ๒๒๓ postoperative recovery after abdominal surgery. *Br. J. Surg.* (2008) 95: 1331-8.
- ๒๒๔ 11. Visalyaputra S, Pethpaisit N, Ariyanon P, Parakkamodom S, Permpolprasert L, Apidechakul
 ๒๒๕ P, Latthikaviboon U, Limsakul A, Santivarangkana T and Sirilertmakasakul P.EMLA cream and
 ๒๒๖ intraperitoneallidocaine decrease intraoperative pain during postpartum tubal sterilization.*J. Med.*
 ๒๒๗ *Assoc. Thai.*(2002)85 Suppl 3:S942-7.
- ๒๒๘ 12. Visalyaputra S, Lertakyamane J, Pethpaisit N, Somprakit P, Parakkamodom S
 ๒๒๙ and Suwanapeum P. Intraperitoneal Lidocaine Decreases Intraoperative Pain During Postpartum
 ๒๓๐ Tubal Ligation. *Anesth.Analg.*(1999)88:1077-80.
- ๒๓๑ 13. Kim T H, Kang H, Hong J H, Park J S, Baek C W, Kim J Y, Jung YH and Kim
 ๒๓๒ HK.Intraperitoneal and intravenous lidocaine for effective pain relief after laparoscopic
 ๒๓๓ appendectomy: a prospective, randomized, double-blind, placebo-controlled study.
 ๒๓๔ *Surgical.Endoscopy.*(2011)25:3183-90.
- ๒๓๕ 14. Lowenstein L, Zimmer E Z, Deutsch M, Paz Y, Yaniv D and Jakobi P. Preoperative
 ๒๓๖ analgesia with local lidocaine infiltration for abdominal hysterectomy pain management. *Eur. J.*
 ๒๓๗ *Obstet. Gynecol. Reprod. Biol.*(2008) 136:239-242.
- ๒๓๘ 15. Williamson KM, Cotton BR and Smith G. Intraperitoneal lidocaine for pain relief after total
 ๒๓๙ abdominal hysterectomy. *Br. J. Anaesth.* (1997) 78: 678-97.
- ๒๔๐ 16. Abdelazim I, Al-Kadi M, El Shourbagy M M, Mohamed A A and Abu fasel M L.
 ๒๔๑ Intraperitoneal lidocaine & tenoxicam for pain relief after gynecological laparoscopy.
 ๒๔๒ *Asian.Pacific.J.Rep.* (2013)2 :146-150.
- ๒๔๓ 17. Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, Mazoit JX, Chauvin M,
 ๒๔๔ Bouhassira D and Fletcher D.Lack of impact of intravenous lidocaine on analgesia, functional
 ๒๔๕ recovery, and nociceptive pain threshold after total hip arthroplasty.*Anesthesiology.*(2008)
 ๒๔๖ 109:118–23.

- ٢٤٧ 18. McCarthy GC, Megalla SA and Habib AS. Impact of intravenous lidocaine infusion on
 ٢٤٨ postoperative analgesia and recovery from surgery: a systematic review of randomized
 ٢٤٩ controlled trials. *Drugs.*(2010)70:1149–63.
- ٢٥٠ 19. Khan MR, Raza R, Zafar SN, Shamim F, Raza SA, Pal KM, Zafar H, Alvi R,
 ٢٥١ Chawla T and Azmi R. Intraperitoneal lignocaine (lidocaine) versus bupivacaine after laparoscopic
 ٢٥٢ cholecystectomy: results of a randomized controlled trial. *J. Surg. Res.* (2012) 178 (2): 662-9.
- ٢٥٣ 20. Bryson GL, Charapov I, Krolczyk G, Taljaard M and Reid D. Intravenous lidocaine does not
 ٢٥٤ reduce length of hospital stay following abdominal hysterectomy. *Can. J. Anaesth.*(2010)
 ٢٥٥ 57:759–66.
- ٢٥٦ 21. Zhang Y, Laster MJ, Eger EI II, Sharma M and Sonner JM. Lidocaine, MK-801, and
 ٢٥٧ MAC. *Anesth. Analg.*(2007) 104: 1098-102.
- ٢٥٨ 22. Vigneault L, Turgeon A F, Co[^]te[^] D, Lauzier F, Zarychanski R, Moore L, Nicole PC
 ٢٥٩ and Fergusson DA. Perioperative intravenous lidocaine infusion for postoperative pain control: a
 ٢٦٠ meta-analysis of randomized controlled trials. *J. Can. Anesth.* (2011) 58:22–37.
- ٢٦١ 23. Shahin A Y and Osman A M. Intraperitoneal lidocaine instillation and postcesarean pain after
 ٢٦٢ parietal peritoneal closure: a randomized double blind placebo-controlled trial. *Clin. J.*
 ٢٦٣ *pain.*(2010) 26: 121-7.
- ٢٦٤ 24-El-Sherbiny W, Saber W, Askalany AN, El-Daly A and Sleem AA. Effect of intra-
 ٢٦٥ abdominal instillation of lidocaine during minor laparoscopic procedures. *Int. J. Gynaecol.*
 ٢٦٦ *Obstet.*(2009)106:213-5.
- ٢٦٧
- ٢٦٨ 25. Pellicano M, Zullo F, Di Carlo C, Zupi E and Nappi C. Postoperative pain control after
 ٢٦٩ microlaparoscopy in patients with infertility: a prospective randomized study. *Fertil. Steril.*(1998)
 ٢٧٠ 70: 289-92.
- ٢٧١ 26-Ahmed BH, Ahmed A, Tan D, Awad ZT, Al-Aali AY, Kilkenny J 3rd, Orlando FA, Al-
 ٢٧٢ Chalabi A, Crass R and Alrawi SJ. Post-laparoscopic cholecystectomy pain: effects of
 ٢٧٣ intraperitoneal local anesthetics on pain control--a randomized prospective double-blinded placebo-
 ٢٧٤ controlled trial. *Am. Surg.*(2008)74:201-9.
- ٢٧٥ 27. Elhakim M, Amine H, Kamel S and Saad F. Effects of intraperitoneal lidocaine combined
 ٢٧٦ with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after
 ٢٧٧ laparoscopic cholecystectomy. *Acta Anaesthesiol. Scand.*(2000)44:929-33.

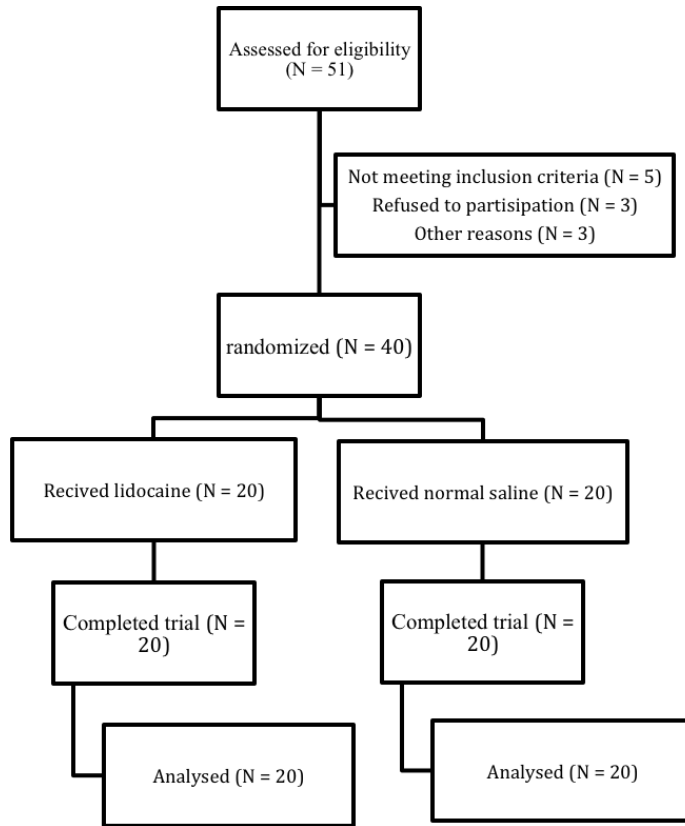
- 278 28. Marks J L, Ata B and Tulandi T. Systematic Review and Metaanalysis of Intraperitoneal
279 Instillation of Local Anesthetics for Reduction of Pain After Gynecologic Laparoscopy. *J. Minim.*
280 *Invasive. Gynecol.* (2012) 19: 545-553.
- 281 29. Kahokehr A, Sammour T, Soop M and Hill A. G. Intraperitoneal local anaesthetic in
282 abdominal surgery – a systematic review. *ANZ. J. Surg.* (2011) 81: 237–245.
- 283 30. Grady M V, Mascha E, Sessler D I and Kurz A. The effect of perioperative intravenous
284 lidocaine and ketamine on recovery after abdominal hysterectomy. *Anesth. Analg.* (2012)
285 115:1078-84
- 286
- 287
- 288

۲۸۹



۲۹۰

۲۹۱



292

293 **Figure 1: Flow of participants**

294

295

٢٩٦ **Table1: Baseline characteristics of participants**

Variable	Lidocaine (N = 20)	Saline (N = 20)	P value
Age (year)	± 3.7244.95	48.20 ± 6.55	0.063
BMI (kg/m ²)	27.25 ± 2.05	28.45 ± 4.56	0.293
History of abdominal surgery	9 (45)	8 (40)	1.0

٢٩٧ *Data are Mean ± SD or numbers (%).

٢٩٨ **Table 2: Comparison of pain scores at different time after total abdominal hysterectomy**
٢٩٩ **between two lidocaine and saline groups**

Time after surgery	Pain score in Lidocaine group (N = 20)	Pain score in Saline group (N = 20)	Mean difference (95% CI)	P value
8 h	7.05 ± 0.95	8.05 ± 0.89	-1.0 (-1.59, -0.41)	0.002
12 h	5.50 ± 1.0	7.15 ± 1.0	-1.65 (-2.30, -1.0)	0.0001
24 h	4.80 ± 0.89	6.10 ± 1.17	-1.30 (-1.96, -0.64)	0.001
48 h	2.95 ± 1.10	3.80 ± 1.20	-0.85 (-1.59, -0.11)	0.038

Comment [D1]: What do you mean please let us know the variable that evaluated in this table

Comment [M2]: In this table we compared pain score between the two groups in each group 20 participants were included (N= 20)

٣٠٠

٣٠١

٣٠٢

٣٠٣