

Effect of intravenous lignocaine on perioperative stress response and post-surgical ileus in elective open abdominal surgeries: a double-blind randomized controlled trial

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Key words

abdominal surgery, ileus, intravenous lignocaine, post-operative pain, stress response.

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Abstract

Background: Perioperative stress response can be detrimental if excessive and prolonged. Intravenous (i.v.) lignocaine, while being an effective analgesic, has the added benefit of anti-inflammatory activity. This study was done to assess the effect of i.v. lignocaine on operative stress response and post-surgical ileus after elective open abdominal surgeries.

Methods: Patients ($n = 134$) were randomized into two groups ($n = 67$ each) to receive an i.v. infusion of lignocaine (group L) or saline (group S) as a bolus of 1.5 mg/kg at intubation followed by an infusion of 1.5 mg/kg/h throughout the surgery until 1 h post-surgery. Total leukocyte count (TLC), C-reactive protein (CRP) and interleukin-6 (IL-6) levels immediately and 24 h after surgery were compared with preoperative levels. Time to first passage of flatus and stools post-operatively was noted. Post-operative pain scores, analgesic requirements, and incidence of post-operative nausea and vomiting (PONV) were assessed in the two groups.

Results: Post-operative surge in TLC, CRP and IL-6 was attenuated in group L as compared to group S ($P < 0.001$, 0.018, <0.001). Time to passage of flatus and stools was earlier in group L ($P = 0.04$, 0.02). PONV was lesser in group L at 6 and 18 h post-surgery (<0.001 , 0.28). Post-operative pain scores and post-operative morphine requirement were significantly less in group L at each point of time post-operatively ($P < 0.001$, <0.001).

Conclusion: Perioperative i.v. lignocaine infusion attenuates the operative stress response, provides effective analgesia and reduces the need for opioids post-operatively. Through these effects, it reduces post-operative ileus and the incidence of PONV.

Introduction

Abdominal surgeries are associated with major alterations in haemodynamic, metabolic and immune responses. Excessive activation of the inflammatory response is responsible for post-operative pain and other undesired side effects like nausea, vomiting and prolonged ileus.¹ Several methods have been employed to reduce this post-surgical stress response like use of opioids,² epidural analgesics,³ melatonin⁴ and dexamethasone.⁵ Intravenous (i.v.)

lignocaine, when used as an infusion in perioperative period apart from producing an effective analgesia, has the added advantage of attenuating the post-surgical stress response through its anti-inflammatory activity.⁶ It leads to a decreased consumption of inhalational anaesthetics and opioids in the perioperative period.⁷ This, in turn, leads to an early recovery of bowel function post-operatively.^{8–10} Though several studies have been done utilizing i.v. lignocaine in abdominal surgeries^{6–10} as an analgesic, there are limited studies^{1,6} assessing the efficacy of lignocaine in reducing the

stress response. Furthermore, its additional benefit of improving bowel function and reducing incidence of post-operative nausea and vomiting (PONV) was not conclusively proven in some previous studies.^{7,8,11} Hence, this study was done to assess the anti-inflammatory activity and bowel function hastening properties of i.v. lignocaine.

Methods

This was a double-blinded randomized placebo-controlled interventional trial done over a period of 15 months on 134 patients undergoing elective open abdominal surgeries in the Department of General Surgery in a tertiary care hospital in South India.

Participants

Patients above 18 years of age, of either gender, undergoing elective open abdominal surgeries, and belonging to the American Society of Anaesthesiologists (ASA) physical status I, II and III were eligible for participation in the trial after obtaining a written informed consent. Patients sensitive to lignocaine, suffering from cardiovascular diseases, on beta blocker drugs, on opioid drugs for prolonged period, and with functional bowel disorders were excluded from this study.

Randomization, allocation concealment and blinding

Patients were randomized into two groups to receive i.v. lignocaine infusion or normal saline (placebo) infusion by block randomization (block size of 10) using Microsoft Excel 2007 (Microsoft Corp, Redmond, WA, USA). Allocation concealment was performed using serially numbered opaque-sealed envelope technique. Envelopes were opened on the day of surgery outside the operating room by an anaesthetist not involved in the research, and the drug solution (L or S) was prepared based on the patient's body weight and administered as an infusion during the surgery. The patients and the investigator who assessed the outcome (pain, ileus) post-operatively were blinded. Hence, this study was double blind. At the end of the study, the groups were decoded and analysed (Fig. 1).

Intervention

A standard anaesthesia and analgesia protocol was used in all patients. Patients in the interventional group received 2% i.v. lignocaine (Xylocard, Neon Laboratories, Mumbai, India) as a bolus dose of 1.5 mg/kg at the time of intubation followed by a continuous infusion at a rate of 1.5 mg/kg/h in the intraoperative period, and continued until 1 h post-surgery. Patients in the control group received an i.v. bolus followed by continuous infusion of 0.9% normal saline (Nirma Laboratories, Ahmedabad, India) at a volume and rate similar to lignocaine until 1 h post-surgery. Post-operatively analgesia was administered through a patient-controlled analgesia (PCA) pump delivering i.v. morphine bolus dose of 1 mg with each demand. Lockout period of 15 min was used to avoid overdosage.

Blood samples for analysis of the levels of total leukocyte count (TLC), and inflammatory mediators like C-reactive protein (CRP) and interleukin-6 (IL-6) were collected in preoperative period immediately after surgery and at 24 h post-surgery. TLC was recorded

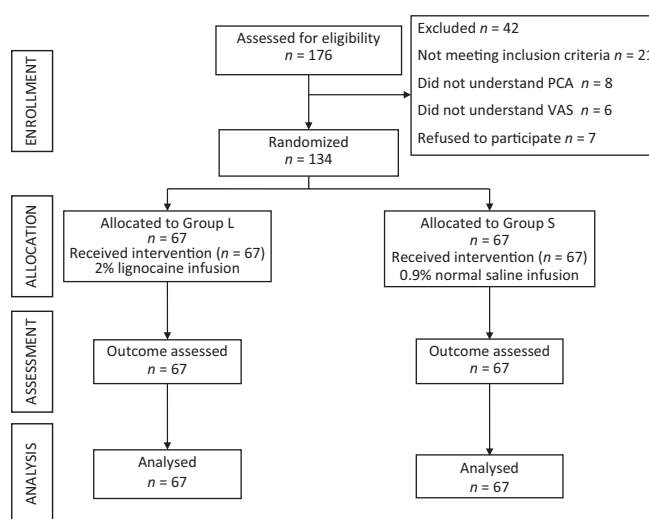


Fig. 1. Flow diagram of the participants through the study. PCA, patient-controlled analgesia; VAS, visual analogue scale.

using an automated calibrating machine (Sysmex XP-300, Sysmex India Pvt Ltd, Mumbai, India). Serum CRP levels were estimated using five high sensitivity CRP kits employing a sandwich-type enzyme-linked immunosorbent assay (ELISA), containing 88 wells each (Diagnostics Biochem Canada Inc, Ontario, Canada). IL-6 levels were analysed in 59 patients in group A and 57 patients in group B using two IL-6 kits containing 176 wells each (BD OptEIA Human IL-6 ELISA kit II, BD Biosciences, San Jose, CA, USA). The time to first passage of flatus and stools post-operatively was noted. Presence of PONV was recorded in the immediate post-operative period and at 6, 18 and 24 h post-surgery on a scale of 0–2 (0 = none, 1 = nausea, 2 = vomiting). Pain was assessed at 1, 6, 18 and 24 h post-surgery using a visual analogue scale (VAS) of 0–10. The time period for the first analgesic requirement through PCA pump post-operatively, the number of PCA demands, and the total dose of morphine consumed in the first 24 h post-surgery were calculated.

Outcomes

The outcomes measured were the perioperative levels of inflammatory mediators (TLC, CRP, IL-6), time to passage of flatus and stools post-operatively, incidence of PONV, post-operative pain scores, time to first analgesic requirement, total number of PCA demands and total dose of morphine consumed during 24-h post-operative period.

Statistical analysis

Statistical analysis was performed using SPSS version 17 for Windows (SPSS, Chicago, IL, USA). Continuous data like age and duration of surgery were compared using independent sample *t*-test of means. Gender distribution and ASA status were compared using chi-square test. The levels of inflammatory mediators like TLC, CRP and IL-6 at each point of time were compared using Mann–Whitney *U*-test. The time to passage of flatus and stools post-operatively was noted and compared using student's *t*-test of comparison of means. The incidence of nausea and vomiting post-operatively was compared using chi-square test and Fisher's exact test. The effect of

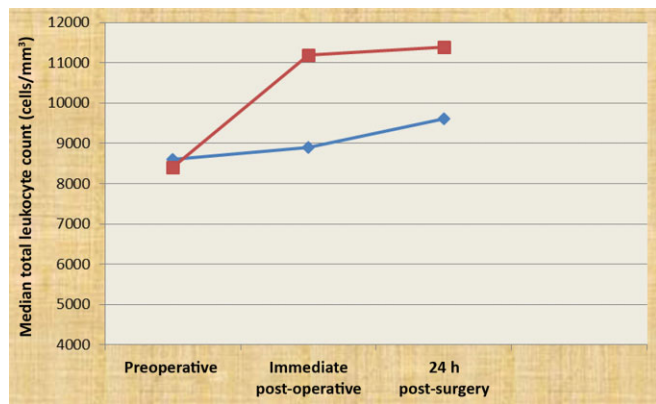


Fig. 2. Chart comparing perioperative total leukocyte counts. (—◆—) group L; (—■—) group S.

lignocaine on post-operative pain was analysed by Mann–Whitney *U*-test comparing the median VAS at each point of study time in the post-operative period. The median time to first analgesic requirement, the median number of PCA demands and the total amount of morphine consumed until 24 h post-surgery were compared using Mann–Whitney *U*-test. A *P*-value < 0.05 was considered statistically significant.

Results

For the purpose of tabulation and analysis, the groups were designated as L and S receiving lignocaine and normal saline infusion, respectively. Both the groups were comparable with respect to demographic parameters and operative characteristics (Table 1). The levels of TLC were significantly attenuated in group L at immediate post-operative and at 24 h post-surgery. The CRP levels in the immediate post-operative period were significantly lesser in group L. The levels of IL-6 were significantly attenuated in group L post-operatively (Figs 2–4). The time to first passage of flatus and stools post-operatively was significantly lesser in the lignocaine group, indicating early recovery from post-surgical ileus in lignocaine group (Table 2). In the immediate post-operative period, there was

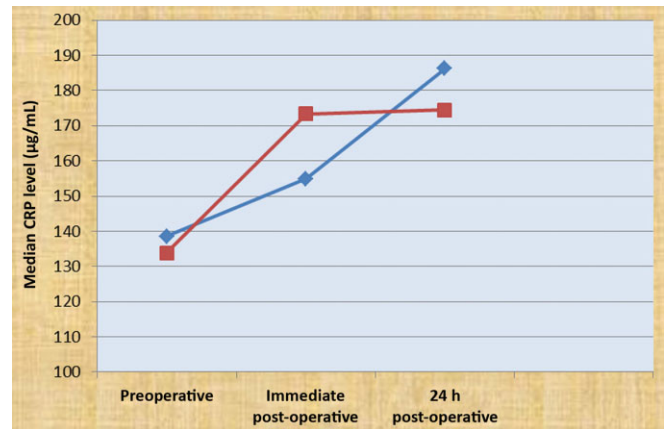


Fig. 3. Chart comparing perioperative C-reactive protein (CRP) levels. (—◆—) group L; (—■—) group S.

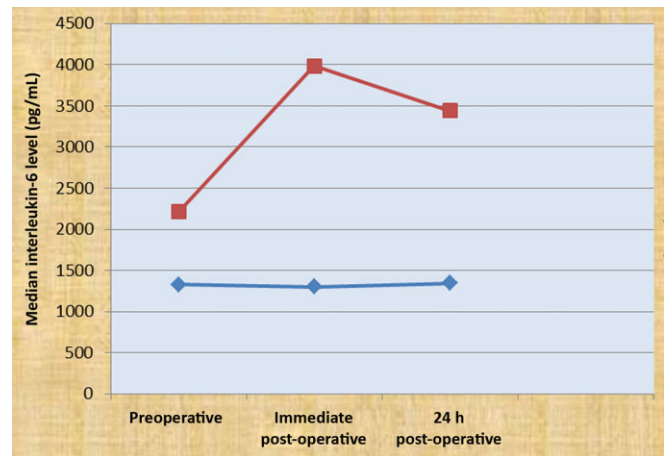


Fig. 4. Chart comparing perioperative interleukin-6 levels. (—◆—) group L; (—■—) group S.

no significant difference in the incidence of PONV between the two groups, but at 6 and 18 h post-surgery it was lower in group L. Anti-emetics were given to patients complaining of nausea post-operatively. The VAS scores in group L were significantly lesser

Table 1 Demographic and operative characteristics

Parameter	Group L (n = 67)	Group S (n = 67)	P-value
Age (mean ± SD) years	49.2 ± 12.8	52.5 ± 15.7	0.19†
Weight (mean ± SD) kg	43.66 ± 8.19	42.43 ± 7.94	0.38†
Male : Female	48:19	43:24	0.35‡
ASA status			
I	39	31	0.064‡
II	27	29	
III	1	7	
Duration of surgery (mean ± SD) in hours	2.43 ± 0.63	2.40 ± 0.75	0.83†
Type of surgery			
Gastrectomy/gastrojejunostomy	24	24	0.65‡
Abdominoperineal resection/anterior resection	11	12	
Cholecystectomy, CBD exploration and other biliary surgeries	13	8	
Others	19	23	

†Student's *t*-test. ‡Chi-square test. ASA, American Society of Anaesthesiologists; CBD, common bile duct.

Table 2 Comparison of post-operative bowel function recovery

Parameter	Group L	Group S	P-value†
Time of passage of flatus (mean ± SD) in hours	48.24 ± 10.33	51.82 ± 9.83	0.042
Time of passage of stools (mean ± SD) in hours	68.45 ± 12.6	73.28 ± 11.45	0.022

†Student's *t*-test.**Table 3** Comparison of post-operative pain scores and analgesic requirement

Parameter		Group L Median (range)	Group S Median (range)	P-value†
VAS	Immediate post-operative	7 (6–8)	8 (7–9)	<0.001
	6 h	4 (3–6)	6 (4–7)	<0.001
	18 h	4 (3–6)	6 (4–6)	<0.001
	24 h	4 (2–5)	5 (3–6)	<0.001
Time to first analgesic requirement (in minutes)		45 (30–60)	30 (15–45)	<0.001
Total number of PCA morphine demands (until 24 h post-operatively)		12 (10–20)	24 (16–34)	<0.001
Total morphine consumption (mg) (until 24 h post-operatively)		10 (8–24)	24 (16–30)	<0.001
Total morphine consumption (in mg/kg) until 24 h post-surgery		0.26 (0.13–0.55)	0.54 (0.38–0.87)	<0.001

†Mann–Whitney *U*-test. PCA, patient-controlled analgesia; VAS, visual analogue scale.

when compared to group S at each point of time in the post-operative period. The time to first analgesic requirement was delayed in group L compared to that in group S. The median total number of PCA demands in the first 24 h post-surgery and the total morphine requirement until 24 h post-surgery were also significantly lower in group L (Table 3).

Discussion

Surgical stress response involves release of various proinflammatory cytokines like IL-6 and CRP.¹² This acute inflammatory response, though beneficial and essential, can be detrimental if excessive and prolonged as can be the case in major open abdominal surgeries. This can result in prolonged post-operative pain, and excessive use of opioid analgesics for pain relief can in turn lead to complications like prolonged post-surgical ileus and PONV. Several methods have been tried to reduce the perioperative stress response.^{2–5} Lignocaine has analgesic and, in addition, anti-inflammatory activity. When given as an infusion in the perioperative period, in addition to providing durable analgesia,^{5,9} it can attenuate the stress response. It decreases surgery-induced peritoneal irritation and suppresses inhibitory sympathetic reflexes during surgery. By providing effective post-operative analgesia and by reducing the opioid analgesic requirement, lignocaine ultimately results in a decreased duration of post-operative ileus.^{6–8} The efficacy of lignocaine as an anti-inflammatory agent and whether the clinical benefits of lignocaine are dependent on the reduced stress response has not been studied extensively and not conclusively proven. There are also controversial results in some studies regarding efficacy of lignocaine in reducing post-surgical ileus and PONV.^{7,8,11} Hence, this study was done to assess the efficacy of lignocaine in terms of these factors. The sample size in our study was higher than that in earlier studies using i.v. lignocaine in abdominal surgeries.^{7–11} Some studies have utilized infusion for a longer duration in the post-operative period and at a higher dose when compared to that of our study.^{1,8,11} In our

study, lignocaine infusion was given throughout the surgery when the stress response is more, and continued until 1 h post-surgery to allow the patient to recover from anaesthesia to utilize the PCA pump effectively.

The anti-inflammatory property of lignocaine has been studied by some authors.^{6,13,14} Though studies done by Kuo *et al.*⁶ in colonic surgeries and Yardini *et al.*¹⁴ in transabdominal hysterectomies found encouraging results, a study done by Kaba *et al.*¹³ in laparoscopic colectomies failed to demonstrate the beneficial effect of lignocaine in reducing cytokine levels. Our study found attenuated levels of IL-6, CRP and TLC in the lignocaine group. Higher inflammatory mediator levels post-operatively can be related to higher pain scores and morphine consumption post-operatively. Hence, by attenuating the surgery-induced stress response, lignocaine can bring about additional pain relief and reduce opioid consumption. Though some authors have reported that patients receiving lignocaine had earlier recovery of bowel function,^{6,9,10} studies done by Koppert *et al.*⁷ and Rimback *et al.*⁸ found no significant effect of lignocaine on ileus. In our study, lignocaine infusion group had lesser duration of ileus as indicated by decreased time to passage of flatus and stools post-operatively. This may partly be due to stress-attenuating property of lignocaine as well as its direct action on inhibiting sympathetic reflexes and its opioid sparing analgesic effect. Though some authors^{6,15} have found lesser incidence of PONV after lignocaine infusion similar to our study, the results are contradictory in some studies.^{5,6,9} This additional beneficial effect of lignocaine can be explained through its bowel function hastening property and its opioid sparing effect. We observed that patients receiving i.v. lignocaine infusion had significantly lesser post-operative VAS scores and lesser opioid analgesic requirement for pain relief as observed in other studies as well. However, some studies^{1,16,17} found no effect of i.v. lignocaine on post-operative pain and recovery of patient. None of the patients in our study had any electrocardiographic abnormalities or neurological side effects due to i.v. lignocaine infusion in the perioperative period. There were no

incidences of anastomotic leak in any patient in our study (34 patients in group L and 35 patients in group S had bowel anastomoses). Other authors have also documented i.v. lignocaine to be safe when given as an infusion even until 24 h post-surgery.^{7,9}

Conclusions

Perioperative i.v. infusion of lignocaine attenuates the operative stress response by reducing the levels of inflammatory mediators released during surgery. It causes a significant reduction in postoperative pain and the need for opioid analgesics post-operatively. The incidence of PONV is decreased and return of bowel function is hastened post-operatively.

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