Clinical Communication

Effect of lignocaine on postoperative serum lactate dehydrogenase and lactate levels in patients undergoing bowel surgery: A randomised controlled trial

INTRODUCTION

Currently, multimodal analgesia and adjunctive therapies are recommended for postoperative pain relief in abdominal surgeries.[1,2] Intravenous (IV) lignocaine is a better alternative for individuals hesitant or not fit to undergo interventional neuraxial and peripheral nerve blocks.[1] Perioperative IV lignocaine has several benefits, including analgesic effects, earlier return of bowel function, decreased postoperative nausea and vomiting (PONV) incidence and shorter hospital stay.[3]

Serum lactate level is used as a marker of balance between demand and available oxygen, leading to an immunoinflammatory response.[4] Postoperative increased lactate levels after major elective abdominal surgery can be linked to an increased risk of postoperative complications and mortality.[4] Pain affects the levels of biochemical markers like lactate dehydrogenase (LDH). The release of inflammatory markers, tissue injury, cell necrosis and damage to tissue architecture are all associated with elevated levels of LDH.[5]

The primary objective of this study was to compare the postoperative serum LDH and lactate levels in patients receiving intraoperative lignocaine versus saline during restoration of bowel surgery under general anaesthesia (GA).

METHODS

This randomised, controlled study was done after approval by the hospital ethics committee (GMCH/IEC/2020/446/36R, dated 16/02/2021) and registration at the Clinical Trials- Registry-India (CTRI/2021/03/032273, dated 24/03/2021, https://www.ctri.nic.in/). The patients were enroled between June 2021 and March 2022. The study complied with the Declaration of Helsinki's ethical principles, 2013 and the Good Clinical Practice. Written informed consent was taken from all participants for study participation and patient data use for research and educational purposes.

Patients of the American Society of Anesthesiologists (ASA) physical status I–II were included in the present study. Patients with neurological disorders, renal or hepatic impairment, inability to understand visual analogue scale (VAS), history of substance abuse, contraindications to study drugs, chronic pain conditions, neurodegenerative or autoimmune disorders, abnormal cardiac conduction or congestive heart failure were excluded from the study.

Baseline haemodynamic data were recorded in the operating room using a multichannel monitor (Aespire View; Datex-Ohmeda, Madison, WI, USA). Serum lactate was measured using a metabolite analyser (blood gas analyser; Radiometer Medical ApS Radiometer Medical Equipment Co. Ltd., Brønshøj, Denmark). LDH was measured using an automated random access chemistry analyser (Clinical Chemistry Analyser; Randox Laboratories Ltd., County Antrim, UK).

Randomisation of the patients was done using a computer-generated random number table, and group allocation concealment was performed by placing the details of group allocation in an opaque sealed numbered envelope:

Group lignocaine (n = 30): Patients received 1.5 mg/kg IV lignocaine 2% followed by infusion at a rate of 1.5 mg/kg/h till the end of surgery.

Group normal saline (n = 30): Patients received 1.5 mg/kg IV normal saline followed by infusion at a rate of 1.5 mg/kg/h till the end of surgery.

The observer (candidate) and the patient were blinded during the study. An independent anaesthesia resident who prepared the study drug did not participate in further analysis and management of the patient.

A standard technique of GA using IV fentanyl 1–2 μg/kg, propofol 2–3 mg/kg, vecuronium 0.1 mg/kg, sevoflurane 1%–2% and nitrous oxide with oxygen (60:40) was followed to maintain a minimum alveolar concentration (MAC) of 1.0. Haemodynamics were kept within 20% of baseline

with balanced anaesthesia, fluid and vasopressors as required. All patients received a standardised fluid therapy of 10–12 ml/kg in the first hour, followed by maintenance fluid therapy of 1.5–2 ml/kg/h.[6] Urine output was maintained at 1 ml/kg/h during the perioperative period. Residual neuromuscular blockade was reversed, and the trachea was extubated after surgery.

In the postoperative period, rescue analgesia with IV tramadol 2 mg/kg was given if the patient experienced a VAS >3 with a maximum dose of 400 mg in 24 h. All patients received IV paracetamol (PCM) 1 g 6 hourly and IV diclofenac 75 mg 12 hourly for 24 h postoperatively.

The primary outcome was to compare serum LDH and lactate levels before surgery (baseline), before tracheal extubation intraoperatively and postoperatively at 6 and 24 h in patients receiving intraoperative lignocaine versus saline during restoration of bowel surgery under GA. Other outcomes measured were VAS at rest and on movement – baseline, 1 h in the postoperative anaesthesia care unit (PACU), and 6, 12 and 24 h after surgery.

Based on the finding that serum LDH concentration was significantly linked with increased postoperative pain [β (standardised regression coefficient) = 0.606, $P < 0.001$],[5] the sample size for the present study was calculated. The sample size (n) was determined using the formula $n = [(Z_\alpha + Z_\beta)/C]^2 + 3$, where standard normal deviate for $\alpha = Z_\alpha = 1.96$, standard normal deviate for $\beta = Z_\beta = 0.84$, $C = 0.5^* \ln[(1 + r)/(1- r)]$ and r is the regression coefficient. Twenty-five subjects comprised our sample, with a power of 0.90 and a 95% confidence interval. It was decided to include 30 patients in each group to account for potential attrition.

The primary outcomes, serum LDH and lactate values were represented as mean (standard deviation [SD]). Secondary outcomes, including demographics, haemodynamic parameters, VAS scores, rescue analgesia used, fluid intake, urine output, patient satisfaction score and arterial blood gas (ABG) parameters, were reported as mean (SD). The *t*-test was utilised for the calculation of pulse rate, blood pressure and respiratory rate, whereas the Mann–Whitney U-test was used for age, weight, height, body mass index (BMI), oxygen saturation, VAS score at rest and on movement, rescue analgesia, fluid intake, urine output, patient satisfaction score, serum LDH and lactate values and ABG parameters. The relationship between serum LDH and lactate values with VAS mean (SD) was analysed using the Spearman/Pearson correlation coefficient. The significance level for each two-sided statistical test was set at $\alpha = 0.05$.

RESULTS

Demographic profile was comparable in the two groups ($P > 0.05$). Values of serum LDH and lactate were lower in Group lignocaine before extubation ($P < 0.001$) and at 6 h ($P < 0.001$) [Table 1].

Postoperative VAS scores at rest [Figure 1a] and on movement [Figure 1b] were lower in Group lignocaine, with statistical significance at all intervals except at 45 min in PACU ($P = 0.062$). A significant correlation was found between LDH and lactate with VAS at rest [Figure 2a and b] and movement [Figure 2c and d] at 6 h. Lactate and LDH at 6 h overall had a moderate positive correlation (rho = 0.54, $P < 0.001$) [Figure 2e].

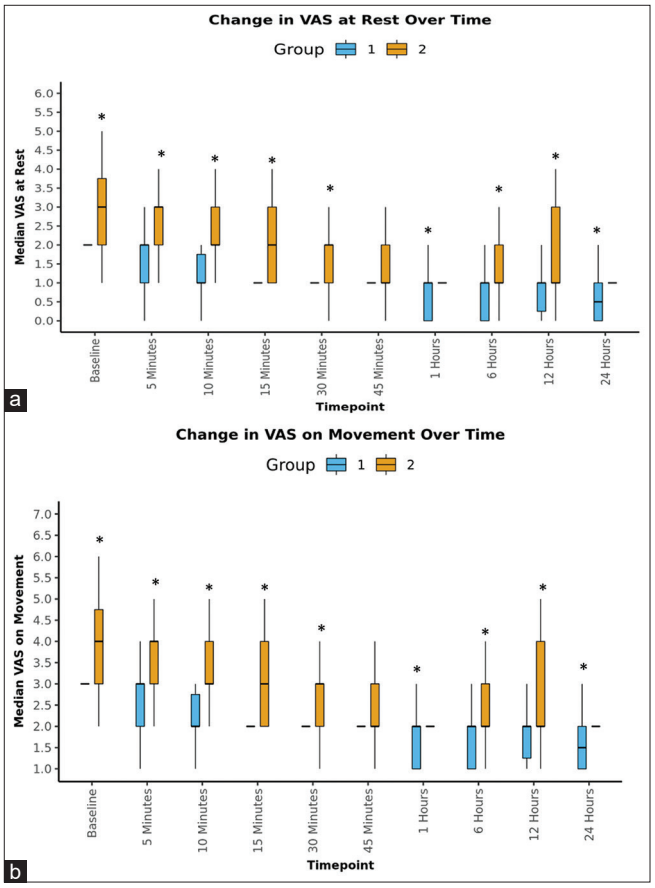

Figure 1: Postoperative comparison of (a) VAS at rest and (b) VAS on movement between Group lignocaine and Group normal saline in patients undergoing bowel surgery. Values are represented as box and whisker plots. VAS = visual analogue scale score

Table 1: Perioperative comparison of LDH and lactate in patients receiving intravenous lignocaine versus normal saline while undergoing bowel surgery

Time interval	Group lignocaine [Serum LDH (IU/l)] (*n*=30)	Group normal saline [Serum LDH (IU/l)] (*n*=30)	*P*	Group lignocaine [Serum lactate (mmol/l)] (*n*=30)	Group normal saline [Serum lactate (mmol/l)] (*n*=30)	*P*
Preoperative	379.79 (172.01) [315.47,443.93]	316.20 (135.97) [265.43,366.97]	0.160	2.79 (0.62) [2.57,3.02]	2.63 (0.96) [2.27,2.99]	0.248
Before extubation	256.43 (117.58) [212.53,300.34]	434.60 (207.83) [357.00,512.20]	<0.001	1.17 (0.38) [1.02,1.31]	2.63 (1.03) [2.24,3.01]	<0.001
6 h	251.63 (91.99) [217.28,285.99]	446.77 (257.84) [350.49,543.05]	<0.001	1.14 (0.63) [0.90,1.38]	2.20 (0.87) [1.87,2.52]	<0.001
24 h	324.77 (130.52) [276.03,373.50]	401.67 (170.40) [338.04,465.30]	0.059	1.15 (0.63) [0.91,1.38]	1.84 (0.58) [1.62,2.05]	<0.001

Data expressed as mean (standard deviation) [95% confidence interval]. LDH=lactate dehydrogenase

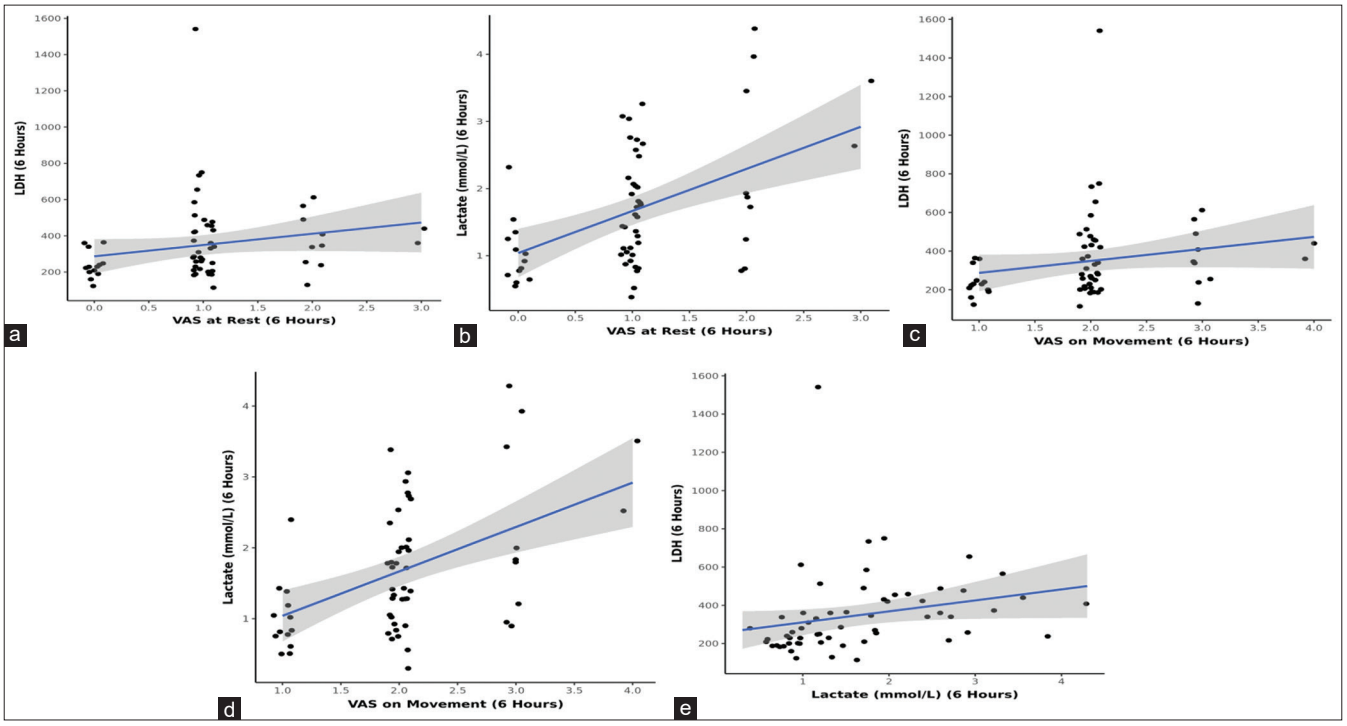

Figure 2: Scatterplot depicting the correlation between (a) VAS at rest (6 h) and LDH (IU/l) (6 h) overall, with a moderate positive correlation, which was statistically significant (rho = 0.34, *P* = 0.008). (b) VAS at rest (6 h) and lactate (mmol/l) (6 h) overall, with a moderate positive correlation, which was statistically significant (rho = 0.44, *P* < 0.001). (c) VAS on movement (6 h) and LDH (IU/l) (6 h) overall, with a moderate positive correlation, which was statistically significant (rho = 0.34, *P* = 0.008). (d) VAS on movement (6 h) and lactate (mmol/l) (6 h) overall, with a moderate positive correlation, which was statistically significant (rho = 0.44, *P* < 0.001). (e) Lactate (mmol/l) (6 h) and LDH (IU/l) (6 h) overall, with moderate positive correlation, which was statistically significant (rho = 0.54, *P* < 0.001). Individual points represent individual cases. The blue trendline represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trendline. LDH = lactate dehydrogenase, VAS = visual analogue scale score

The consumption of IV tramadol as rescue analgesia was lower in Group lignocaine in PACU ($P < 0.001$) and at 12 h ($P = 0.010$). Patient satisfaction score mean (SD) [95% confidence interval (CI)] at 24 h was statistically superior in Group lignocaine 4.93 (0.25) [4.84–5.03] compared to Group normal saline 4.67 (0.48) [4.49–4.85] ($P = 0.010$).

The ABG parameters were constant, comparable and within normal physiological bounds for both groups. Haemodynamics in both groups remained within the physiological range. No adverse effects were noted.

DISCUSSION

The novelty of the present study is that we have demonstrated that LDH and lactate levels are reduced with IV lignocaine. The scientific data supporting the same is the published literature that reports pain hypersensitivity due to acidic microenvironments with lactic acid production in anaerobic situations.[7-9]

Inflammatory insult to tissues causes recruitment of neutrophils and macrophages. Increased activity of pyruvate dehydrogenase kinase (PDK) 2 and PDK4 in neutrophils and macrophages after a stimulus causes phosphorylation/inhibition of pyruvate dehydrogenase, leading to increased lactate production. This acidic microenvironment favours the recruitment of more inflammatory cells, and increases localised inflammation that causes nociceptive reactions. Increased levels of lactate and pro-algesic signals cause peripheral sensitisation of the dorsal root ganglion and central sensitisation of the spinal cord via inflammatory mediators, leading to increased pain hypersensitivity.[10,11]

A strong association was found between LDH concentrations and postoperative pain. LDH as a biochemical predictor may be used to identify patients who need more potent analgesics for aggressive pain management following surgery.[5]

The analgesic effect of IV lignocaine can be understood via the peripheral and central nervous systems. IV lignocaine decreases the influx of macrophages and neutrophils at the site of inflammation, thereby suppressing the rise in levels of proinflammatory cytokines and decreasing the formation of lactate, leading to adequate pain relief.[12,13] Lignocaine suppresses the activity of neural glial cells, causing reduced pain hypersensitivity and release of inflammatory mediators.[14] This mechanism can probably explain the novelty of the present study as it demonstrates lower LDH and lactate with lower pain scores in patients receiving IV lignocaine infusion during restoration of bowel continuity surgery.

There were a few limitations in the present study. The present study was a single-centre study and included only patients with ASA physical status I and II. The entropy measurement was not included in the present study. Multicentric studies or studies with larger sample sizes will be desired to fill the knowledge gaps.

CONCLUSION

The postoperative serum LDH and lactate levels were lower in patients receiving intraoperative IV lignocaine compared to normal saline in patients undergoing bowel surgery.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest

There are no conflicts of interest.

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