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RESEARCH ARTICLE

EFFECT OF INTRAOPERATIVE N-ACETYLCYSTEINE AND EXCESS FLUID ADMINISTRATION ON LIVER ENZYMES AND BLOOD PH DURING LAPAROSCOPIC SLEEVE GASTRECTOMY

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ABSTRACT

Background/aim: To investigate the protective role of intraoperative infusion of N-acetylcysteine (NAC), and excess fluid on liver injury and blood pH levels during laparoscopic sleeve gastrectomy.
Materials and Methods: Forty-five consecutive patients who underwent laparoscopic sleeve gastrectomy for treatment of obesity between september 2016-june 2017 were randomized into three groups each with 15 patients: Group 1 (control group) was applied neither NAC intraoperatively, Group 2: 10 mg/kg intravenous NAC and 30 mL/kg fluid, and Group 3: 30 mg/kg NAC and 50 mL/kg fluid intraoperatively. The fluid was ringer lactate and normal saline in 1:1 ratio. Biochemical markers of liver function and metabolic acidosis were evaluated.
Results: Blood levels of AST, ALT increased significantly with the operation ($p<0.001$). The increase in AST was significantly higher in Group 3 compared to Group 1 ($p=0.046$). HCO_3 and pH were within normal range preoperatively, but significantly decreased indicating development of primary metabolic acidosis in all groups. The decrease in both HCO_3 and pH was significantly less in Group 3 than Group 1 ($p<0.05$).
Conclusion: Intraoperative infusion of 30 mg/kg NAC and 50 mL/kg fluid during laparoscopic sleeve gastrectomy may reduce liver injury and prevent metabolic acidosis, thus should be considered during surgical management of morbidly obese patients.

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INTRODUCTION

Laparoscopic sleeve gastrectomy is a restrictive bariatric surgery that was used for the treatment of obesity (Benaiges *et al.,* 2015). It is the second most commonly applied technique after Roux-en-Y gastric bypass, which is the current gold standard in bariatric surgery (Buchwald, 2011). Laparoscopic sleeve gastrectomy induces weight loss and improves carbohydrate metabolism by accelerating gastric emptying and intestinal transit (Abbatini *et al.,* 2010; Chambers *et al.,* 2014). It is a very effective surgical technique providing up to 67% excess percentage weight loss in morbid obese patients during 12 months after surgery (Li, 2014). Although advances in laparoscopic surgery provided a significant reduction in bariatric surgery-related mortality (Hutter, 2011), technical differences among surgeries may cause complications unique to each technique. The most common complication of laparoscopic sleeve gastrectomy is staple line leak, of which various approaches have been proposed for the management (Csendes *et al.,* 2010).

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Liver injury is a much less frequent but a serious complication of laparoscopic sleeve gastrectomy, which occurs due to intraoperative retraction of the hypertropic and fatty left lobe of the liver (Belgaumkar *et al.,* 2016). Various techniques have been suggested in order to obtain an effective and safe liver retraction, each having particular disadvantages (Shimizu *et al.,* 2014; Genser *et al.,* 2016; de la Torre, 2015). N-acetylcysteine (NAC) is a precursor of glutathione and acts as an antioxidant with a free radical scavenger activity and anti-inflammatory agent increasing production of endothelial nitric oxide synthase. It has been used as a mucolytic drug and supplementary treatment in several disorders caused by generation of free oxygen radicals such as such as chronic bronchitis, polycystic ovary, preterm birth, ulcerative colitis, and liver cancer (Mokhtari, 2017). NAC has been shown to have a protective role of against chronic cholestasis-induced liver injury in rats (Gunay, 2014). It may also improve liver function in patients with non-alcoholic fatty liver disease (Khoshbaten *et al.,* 2010). However, there are few studies on the effect of intraoperative NAC on liver injury during laparoscopic sleeve gastrectomy (Belgaumkar *et al.,* 2016). It has also been known that morbid obese patients are also under risk of postoperative rhabdomyolysis, which is destruction of

skeletal muscle classically presented as marked elevation of serum creatine kinase (Chavez *et al.,* 2016). Intravenous fluid therapy is the key treatment of rhabdomyolysis (Chatzizisis *et al.,* 2008). Along with rhabdomyolysis, risk of metabolic acidosis also increases in bariatric surgery as a complication of anesthesia (Lehavi, 2015). We suggest that excess intravenous fluid therapy and NAC infusion together may be protective against postoperative rhabdomyolysis and metabolic acidosis. Therefore, in this study we aimed to investigate the protective role of intraoperative infusion of NAC and excess fluid administration on liver injury and arterial blood pH levels during laparoscopic sleeve gastrectomy.

METHODS

Study design and population

This was a prospective randomized study in which 45 consecutive patients (33 females, 12 males) who had body mass index (BMI) of more than 35 kg/m^2 and underwent laparoscopic sleeve gastrectomy for treatment of obesity in Sanko University Faculty of Medicine Department of General Surgery between september 2016-june 2017 were included. Exclusion criteria were previous gastric or intestinal surgery, any medical contraindication for surgical intervention, active gastric disease, pregnancy or lactation, known intolerance to NAC, high levels of preoperative liver enzymes, and active infection. Patients were randomized into three groups each with 15 patients: Group 1 (control group; mean age 29.7±6.6 years, BMI 44.7±2.9 kg/m^2) was given 30 ml/kg fluid without NAC, Group 2 (mean age 30.6 ±8.5 years, BMI 44.7±4.0 kg/m^2) was given 10 mg/kg intravenous NAC (Assist 300 mg/3 ml Solution, Bilim Pharmaceuticals, Istanbul, Turkey) and 30 ml/kg fluid, and Group 3 (mean age 29.6±6.1 years, BMI 44.2±3.4 kg/m^2) was given 30 mg/kg NAC and 50 ml/kg fluid intraoperatively.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Ethics Committee of Sanko university Faculty of Medicine (No 2017/1-6, Date 24.01.2017). Informed consent was obtained from all individual participants included in the study.

Surgical procedure and outcome measures

The same surgical method was applied by the same surgical team. All patients received propofol rocuronium and fentanyl for standard anesthesia, and sevoflurane inhalation and remifentanil infusion for manitenance. For intravenous access, 16G cannula was inserted. With the patient in the reverse Trendelenburg position the procedure was applied with the method of placing 5 trochars in the French position. The abdomen was inflated with internal 14mmHg carbon dioxide and the stomach was mobilised by cutting the gastrocolic and gastrosplenic ligaments with a 5 mm LigaSure (Covidien, Dublin, Ireland) starting from approximately 4cm prepyloric. At this stage, methylene blue was administered to the patients. After resection was completed, the orogastric tube was removed as far as the oesophagogastric junction, the pylorus was closed with long intestinal forceps and methylene blue was administered until fully circulated in the remnant stomach. In patients determined with leakage, the whole staple line was sutured with 2/0 non-absorbable sutures. The leakage test was then repeated. The stomach tissue was extracted from the prepyloric incision. A drain was placed in all patients. NAC was administered in 100 ml saline within 30 min just after gastrectomy. The fluid was the mixture of the ringer lactate and normal saline in 1:1 ratio. Of the calculated amont of fluid, 1000 ml was loaded 1 hour before the operation, and the remaining amount was given intraoperatively. Blood samples were obtained 1 hour before the surgery (preoperation), after trocars removal and before extubation (intraoperation), and 24 hours after the surgery (postoperation). In order to evaluate the hepatocellular injury and metabolic acidosis during laparoscopic sleeve gastrectomy, the level of following parameters was determined in patients' blood samples: aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), lactate (LAC), creatine kinase, and urine output. Arterial blood gas samples were collected just before surgery, after removal and 30 min after extubation in post-anesthesia care unit. The standard postoperative follow-up was performed, and patients were discharged from the hospital after starting oral diet.

Statistical analysis: The study data were summarized using descriptive statistics such as mean, median, standard deviation, range, frequency and percentage. Statistical analysis was performed using SPSS 22.0 (IBM Corparation, Armonk, New York, USA) and PAST 3 (Øyvind Hammer, Natural History Museum, University of Oslo, Oslo, Norway). Shapiro-Wilk test and Mardia test were used to test for normality of distribution of univariate and multivariate data, respectively. The homogeneity of variance was assessed by the Levene test. For comparison of continuous data of three groups, one-way analysis of variance (ANOVA) with post hoc Games-Howell test was used for data with normal distribution, nonparametric Kruskal-Wallis test with post hoc Dunn's test was used for data with not normal distribution.

The significance of the change in repeated measurements was tested by Wilcoxon Signed Ranks test for two measurements and Friedman's Two-Way test for more than two measurements, both with post hoc Dunn's testi kullanıldı. The effect of study groups on the repeated measures was evaluated by the general linear model-repeated ANOVA test with post hoc Bonferonni test. The comparison of categoric variables was performed by the Pearson Chi-Square test. The correlation between study parameters was assessed by the Spearman's rho test. Statistical level of significance was set to $p<0.05$.

RESULTS

The study groups were comparable with respect to gender and BMI. Although the mean age of Group 3 was significantly lower than Group 1 and Group 2 ($p<0.001$), age difference between groups was not clinically significant (Table 1). Blood levels of AST and ALT were similar between groups before the laparoscopic sleeve gastrectomy ($p>0.05$), and increased significantly after the operation ($p<0.001$) (Table 2). Although the amount of increase in ALT level with the operation did not show significant difference between groups, the increase in AST was significantly lower in Group 3 compared to Group 1 ($p=0.046$, Figure 1). LDH, creatine kinase, and urine output were also similar between groups before the operation showing significant and comparable increase in all groups during and after the operation ($p<0.001$, Table 2).

Table 1. Basic clinical characteristics of study groups

		Group 1 (n=15)	Group 2 (n=15)	Group 3 (N=15)	p value
Age (years)		29.73±6.61	30.60±8.56	25.60±6.12	<0.001[a]
Gender	Female	11 (73.3%)	12 (80.0%)	10 (66.7%)	0.906[b]
	Male	4 (26.7%)	3 (20.0%)	5 (33.3%)	
BMI (mg/kg^2)		44.78±2.92	44.70±4.06	44.25±3.42	0.446[a]
Urine (intraoperative volume/ml)		136.00±29.72	226.00±47.46	273.33±30.36	<0.001[c]

[a] Kruskal Wallis test. Post hoc Dunn's test shows p<0.001 for Group 1 vs. Group 3 and Group 2 vs. Group 3.
[b] Pearson chi-square test.
[c] Kruskal-Wallis test. Post hoc Dunn's test shows p<0.001 for Group 1 vs. Group 2, Group 1 vs. Group 3, and Group 2 vs. Group 3.
Data are given as mean±standard deviation or n (%). BMI, body mass index

Table 2. Biochemical parameters of the study groups during the study

		Group 1 (n=15)	Group 2 (n=15)	Group 3 (n=15)	p value
ALT (U/L)	Preoperation	22 (89–9)	23 (61–10)	24 (30–16)	0.832[a]
	Postoperation	86 (403–24)	66 (281–23)	54 (114–22)	0.176[a]
	p value[d]	<0.001	<0.001	<0.001	
AST (U/L)	Preoperation	19 (29–7)	19 (31–10)	22 (32–12)	0.468[a]
	Postoperation	72 (286–25)	52 (154–24)	42 (96–25)	0.068[a]
	p value[d]	<0.001	<0.001	<0.001	
LDH (U/L)	Preoperation	154 (196–101)	141 (164–122)	136 (324–78)	0.498[a]
	Intraoperation	173 (207–149)	183 (198–149)	165 (302–61.43)	
	Postoperation	222 (278–170)	223 (253–176)	201 (286–112)	
	p value[e]	<0.001	<0.001	<0.001	
Lactate (mmol/L)	Preoperation	1.9 (2.2–1.2)	1.4 (1.9–1.1)	1.6 (1.9–1.2)	0.014[b]
	Intraoperation	1.8 (2.4–1.4)	1.6 (2.4–1.4)	1.6 (2.9–1.2)	
	Postoperation	1.9 (2.5–1.4)	1.9 (2.6–1.5)	1.6 (2.7–1.2)	
	p value[e]	0.466	<0.001	0.774	
Creatine kinase (U/L)	Preoperation	113.67±30.14	105.33±20.02	99.80±35.91	0.437[c]
	Intraoperation	172.40±76.64	147.87±37.48	139.60±54.95	
	Postoperation	205.73±92.65	184.40±44.86	205.93±144.47	
	p value[e]	0.003	<0.001	0.001	
Urine output (ml/kg/h)	Preoperation	5.47±0.84	5.46±1.14	4.69±1.35	0.111[c]
	Intraoperation	7.19±0.96	6.75±1.37	6.03±1.64	
	Postoperation	7.77±1.17	7.67±1.30	7.11±1.54	
	p value[e]	<0.001	<0.001	<0.001	

[a] Kruskal-Wallis test.
[b] Kruskal-Wallis test. Post hoc Dunn's test shows p=0.035 for Group 1 vs. Group 2 and p=0.047 for Group 1 vs. Group 3.
[c] One way ANOVA
[d] Wilcoxon signed ranks test
[e] Friedman's test
Data are given as median (range) or mean±standard deviation.

Table 3. Metabolic acidosis parameters of the study groups during the study

		Group 1 (n=15)	Group 2 (n=15)	Group 3 (n=15)	p value[l]
pH	Preoperation	7.37±0.03	7.37±0.02	7.37±0.03	0.996[c]
	Intraoperation	7.30±0.03	7.31±0.03	7.33±0.03	
	Postoperation	7.33±0.02	7.35±0.02	7.35±0.02	
	p value[f]	<0.001	<0.001	0.001	
HCO_3 (mmol/L)	Preoperation	24.2 (24.4–22.7)	24.2 (24.9–23.6)	24.2 (25.1–20)	0.681[a]
	Intraoperation	18.1 (22.9–17.2)	21.6 (23.4–17.2)	22.2 (24.1–18.4)	
	Postoperation	21 (23.9–20)	23.7 (24.1–21.1)	23.9 (24.7–19.7)	
	p value[e]	<0.001	<0.001	<0.001	
$PaCO_2$ (mmHg)	Preoperation	36.1 (37–34.6)	36.2 (37.4–35.4)	36.9 (38.1–35.1)	0.003[b]
	Intraoperation	41.3 (52.6–37.4)	40.9 (43.9–37.1)	39.1 (43.2–35.4)	
	Postoperation	38.7 (44.3–36.4)	38 (41.2–36.4)	38.1 (41.6–35.9)	
	p value[e]	<0.001	<0.001	<0.001	
Base excess	Preoperation	4.2 (4.6–4)	4.2 (4.7–4.1)	4.6 (5.6–4.1)	0.001[d]
	Intraoperation	11.3 (14.1–5.2)	9.6 (13.2–6.2)	5.9 (8–4.8)	
	Postoperation	6.4 (9.2–4.7)	6.7 (8.4–4.9)	5.3 (6.4–4.1)	
	p value[e]	<0.001	<0.001	<0.001	

[a] Kruskal-Wallis test.
[b] Kruskal-Wallis test. Post hoc Dunn's test shows p=0.003 for Group 1 vs. Group 3.
[c] One way ANOVA
[d] Kruskal-Wallis test. Post hoc Dunn's test shows p=0.009 for Group 1 vs. Group 3 and p=0.002 for Group 1 vs. Group 3.
[e] General linear model-repeated ANOVA.
[f] Friedman's test
Data are given as median (range) or mean±standard deviation.

HCO_3 and pH were within normal range in all study groups before the operation, but significantly decreased indicating development of primary metabolic acidosis in all groups (Table 3).

The decrease in both HCO_3 and pH was significantly less in Group 3 compared to Group 1 ($p<0.05$, Figure 2). $PaCO_2$ significantly increased during and after the operation in all groups but still remained within normal limits (Table 3).

Table 4. Spearman's rho correlation coefficient (r) for the correlation between blood pH and biochemical parameters of the study groups during the study

		Group 1 (n=15)						Group 2 (n=15)						Group 3 (n=15)					
		Preop		Intraop		Postop		Preop		Intraop		Postop		Preop		Intraop		Postop	
		r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
AST	Preop	-0.220	0.432	-0.048	0.865	-0.019	0.946	0.063	0.824	0.187	0.505	0.075	0.790	*-0.674*	*0.006*	-0.485	0.067	-0.404	0.135
	Postop	-0.220	0.430	-0.427	0.112	-0.315	0.253	0.391	0.150	-0.375	0.168	-0.337	0.219	0.075	0.791	-0.064	0.821	0.087	0.758
ALT	Preop	-0.075	0.791	0.012	0.967	-0.169	0.546	0.168	0.549	0.083	0.770	0.148	0.598	-0.344	0.210	-0.480	0.070	-0.373	0.171
	Postop	-0.060	0.831	-0.445	0.096	-0.181	0.518	0.242	0.385	-0.359	0.189	-0.301	0.276	-0.009	0.975	-0.238	0.394	-0.069	0.806
LDH	Preop	-0.110	0.696	-0.249	0.371	-0.270	0.331	0.109	0.699	-0.178	0.526	-0.200	0.475	-0.320	0.244	-0.331	0.228	-0.307	0.266
	Intraop	0.186	0.508	-0.290	0.294	-0.132	0.639	-0.133	0.636	*-0.556*	*0.031*	*-0.522*	*0.046*	-0.306	0.267	-0.212	0.448	-0.214	0.443
	Postop	0.164	0.559	0.118	0.676	-0.006	0.982	0.016	0.954	-0.477	0.072	-0.418	0.121	-0.227	0.416	-0.113	0.687	-0.258	0.353
Lactate	Preop	*-0.652*	*0.008*	*-0.683*	*0.005*	*-0.930*	*<0.001*	-0.061	0.830	-0.469	0.078	-0.317	0.250	0.166	0.555	0.106	0.706	0.203	0.469
	Intraop	-0.006	0.984	-0.513	0.051	-0.287	0.300	-0.356	0.192	-0.391	0.149	-0.456	0.088	*-0.614*	*0.015*	-0.410	0.129	-0.492	0.063
	Postop	*-0.592*	*0.020*	-0.454	0.089	*-0.712*	*0.003*	0.013	0.964	*-0.729*	*0.002*	*-0.728*	*0.002*	-0.329	0.231	0.130	0.644	-0.136	0.629
Creatinine kinase	Preop	*-0.526*	*0.044*	-0.471	0.076	*-0.734*	*0.002*	0.039	0.890	*-0.869*	*<0.001*	*-0.767*	*0.001*	-0.247	0.375	0.197	0.482	0.006	0.982
	Intraop	-0.352	0.198	*-0.663*	*0.007*	*-0.593*	*0.020*	0.216	0.439	*-0.740*	*0.002*	*-0.700*	*0.004*	-0.122	0.664	0.298	0.281	0.042	0.882
	Postop	-0.151	0.592	*-0.632*	*0.011*	-0.422	0.117	0.178	0.526	*-0.772*	*0.001*	*-0.722*	*0.002*	-0.155	0.582	0.192	0.493	-0.093	0.741
Urine output	Preop	0.084	0.766	0.046	0.870	-0.154	0.583	-0.189	0.499	-0.251	0.367	-0.186	0.508	-0.338	0.219	0.329	0.231	-0.015	0.959
	Intraop	0.039	0.890	-0.482	0.069	-0.247	0.375	-0.309	0.262	-0.395	0.145	-0.337	0.219	-0.380	0.163	0.289	0.296	-0.039	0.889
	Postop	0.131	0.642	-0.406	0.133	-0.183	0.513	-0.094	0.739	-0.450	0.093	-0.416	0.123	-0.167	0.551	0.349	0.202	0.004	0.990

Table 5. Spearman's rho correlation coefficient (r) for the correlation between blood pH and metabolic acidosis parameters of the study groups during the study

		Group 1 (n=15)						Group 2 (n=15)						Group 3 (N=15)					
		Preop		Intraop		Postop		Preop		Intraop		Postop		Preop		Intraop		Postop	
		r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
HCO_3	Preop	0.092	0.744	*0.771***	*0.001*	*0.229*	*0.411*	-0.157	0.577	*0.724***	*0.002*	*0.711***	0.003	0.268	0.334	0.312	0.257	0.303	0.272
	Intraop	0.500	0.057	*0.666***	*0.007*	*0.836***	*<0.001*	-0.123	0.662	*0.743***	*0.002*	*0.760***	0.001	0.165	0.556	-0.046	0.871	-0.017	0.951
	Postop	0.146	0.604	*0.816***	*<0.001*	0.479	0.071	-0.303	0.272	*0.603**	*0.017*	*0.627**	0.012	0.212	0.449	0.119	0.674	0.078	0.782
$PaCO_2$	Preop	-0.330	0.230	0.263	0.344	-0.133	0.637	0.195	0.487	-0.257	0.355	-0.271	0.329	-0.050	0.861	-0.143	0.612	-0.213	0.447
	Intraop	-0.040	0.888	0.017	0.951	-0.007	0.979	0.299	0.278	-0.490	0.064	-0.470	0.077	-0.165	0.557	-0.229	0.413	-0.417	0.122
	Postop	0.118	0.675	0.207	0.459	0.225	0.420	0.117	0.677	-0.409	0.130	-0.389	0.151	-0.149	0.595	-0.341	0.214	-0.449	0.093
Base excess	Preop	0.024	0.933	-0.006	0.982	-0.070	0.804	0.189	0.499	-0.385	0.156	-0.366	0.180	-0.127	0.651	-0.305	0.269	-0.145	0.606
	Intraop	-0.247	0.375	-0.145	0.606	-0.418	0.121	0.287	0.300	-0.428	0.112	-0.462	0.083	-0.236	0.397	*-0.629**	*0.012*	-0.492	0.062
	Postop	-0.014	0.962	0.093	0.743	0.071	0.800	-0.034	0.905	*-0.595**	*0.019*	*-0.609**	0.016	-0.198	0.479	*-0.721***	*0.002*	*-0.572**	*0.026*

The increase in $PaCO_2$ was significantly less in Group 3 compared to Group 1 (p=0.002). Base excess, which was significantly lower in Group 3 than Group 1 and Group 2 preoperatively, decreased significanlty during and after the laparoscopic sleeve gastrectomy in all groups (Table 3).

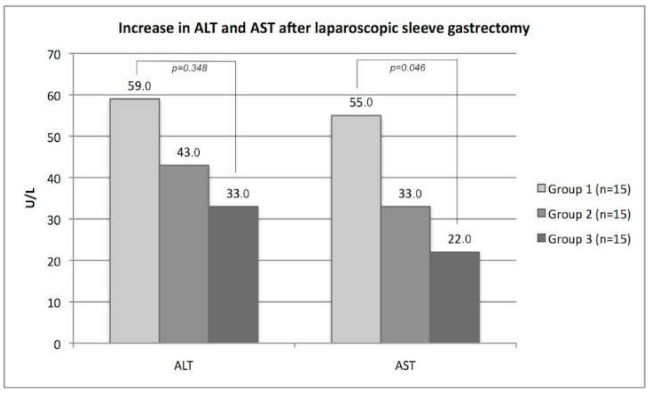

Figure 1. Blood levels of AST and ALT increased significantly after the laparoscopic sleeve gastrectomy operation. The amount of increase in ALT level with the operation (*difference between postoperative and preoperative levels*) did not show significant difference between groups, as the increase in AST was significantly higher in Group 3 compared to Group 1 (p=0.046).
Group 1, control group
Group 2, 10 mg/kg N-acetylcysteine+30 ml/kg fluid
Group 3, 30 mg/kg N-acetylcysteine+50 ml/kg fluid

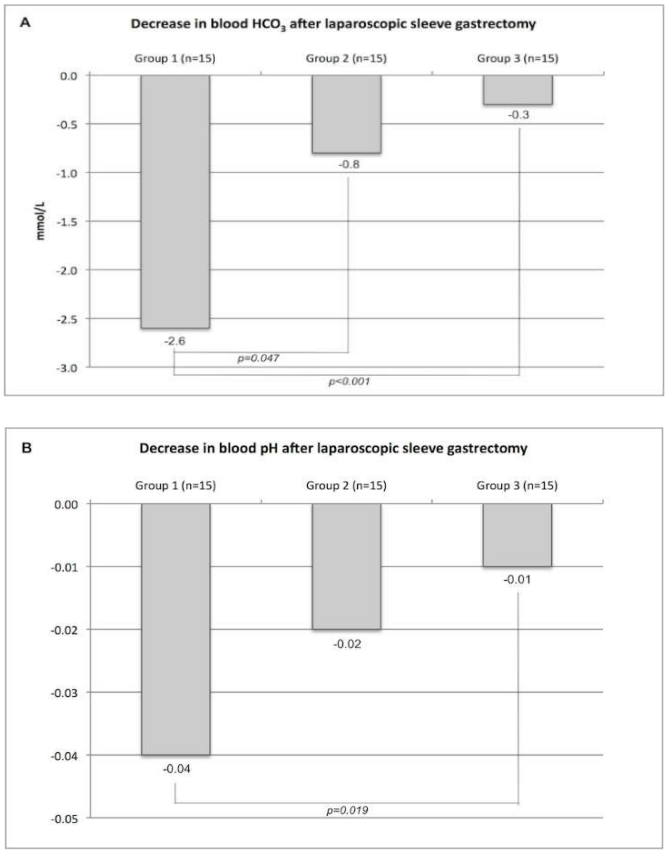

Figure 2. Blood levels of HCO_3 (A) and pH (B) decreased significantly after the laparoscopic sleeve gastrectomy operation. Group 3 had significantly less decrease in both HCO_3 and pH (*difference between postoperative and preoperative levels*) than Group 1 (p<0.001 and p=0.019, respectively), as Group 2 had significantly less decrease in HCO_3 than Group 1 (p=0.047).
Group 1, control group
Group 2, 10 mg/kg N-acetylcysteine+30 ml/kg fluid
Group 3, 30 mg/kg N-acetylcysteine+50 ml/kg fluid

The decrease in base excess was significantly less in Group 3 than other two groups (p<0.001). Spearman's rho correlation analysis revealed that blood pH was negatively correlated with blood lactate, creatine kinase and LDH levels and positively with HCO_3 levels in Group 1 and Group 2 (Tables 4 and 5).

DISCUSSION

Since bariatric surgery has been performed through smaller incisions and fewer ports, injury of left lobe of liver became an increasing complication of the surgery. In this prospective randomized study, we primarily showed that intraoperative infusion of 30 mg/kg NAC and 50 mL/kg fluid during laparoscopic sleeve gastrectomy may reduce liver injury and prevent metabolic acidosis. Since NAC and fluid infusion is very easy and practical applications without any side effect and additional intervention, it should be considered during surgical management of morbidly obese patients for prevention of intraoperative liver injury, which can lead to serious consequences. Some previous studies suggested the use of antioxidative agents like vitamin C or E for protection against liver injury (Oliveira, 2003). Therefore, we suggested that intraoperative injection of an antioxidative agent may provide protection against liver injury in laparoscopic sleeve gastrectomy. The liver function paramaters evaluated in the present study were AST, ALT, LDH, and LAC, high levels of which indicate hepatic injury (Sirikutt, 2014). Overall preoperative evaluation through these parameters showed that our study population had no liver dysfunction. However, serum ALT, AST, and LDH leves increased significantly after the operation in all study groups (p<0.001), which suggest that intraoperative NAC and excess fluid was not able to reverse sleeve gastrectomy-induced increase in liver enzymes. On the other hand, although the amount of change in ALT, LDH and LAC levels with the operation did not show significant difference between groups, the increase in AST was significantly lower in Group 3 compared to Group 1 (p=0.046). This finding may suggest that intraoperative infusion of 30 mg/kg NAC and 50 mL/kg fluid may reduce liver injury during laparoscopic sleeve gastrectomy. This was contrary to the findings of a previous study by Belgaumkar *et al*. (2016) which reported that NAC did not reduce intraoperative liver injury in a sample of 20 patients. The different findings between studies may be due to heterogenous nature of study populations, dosing of NAC, and small sample sizes. On the basis of our findings, we suggest that intraoperative infusion of NAC has a potential usage during laparoscopic sleeve gastrectomy, which needs to be confirmed with further large-scale comparative studies.

In the correlation analysis, blood pH was negatively correlated with blood lactate, creatine kinase, and LDH levels and positively with HCO_3 levels in Group 1 and Group 2, which was a finding indicating that tissue damage due to restricted oxygenation leads to increase in the levels of creatine kinase, LDH and lactate, which then decreases the blood pH. The lack of correlation between blood pH and biochemical tissue destruction parameters in Group 3 may be considered as an indicator of protective effect of intraoperative infusion of 30 mg/kg NAC and 50 mL/kg fluid during laparoscopic sleeve gastrectomy on liver injury and metabolic acidosis. Various types of intravenous fluids such as 5% dextrose, normal saline, ringer lactate, and their combination have been suggested to be used for prevention and treatment of rhabdomyolysis (Chavez *et al.,* 2016; Cho, 2007).

We applied the mixture of the ringer lactate and normal saline in 1:1 ratio as intravenous fluids. Serum creatine kinase levels, which is an idicator of rhabdomyolysis, increased in all study population but remained within normal limits during study without showing significant difference between study groups. Since increase in serum creatine kinase five to ten times the upper limit of normal serum levels indicates rhabdomyolysis (Chavez *et al.,* 2016), no evident intra- or postoperative rhabdomyolysis develeoped in any of study groups. Therefore, we could not conclude on the protective effect of excess fluid against rhabdomyolysis on the basis of our findings. The main limitation of our study was its small sample size, which precludes us from reaching a definitive conclusion on the preventive effect of intraoperative infusion of NAC and excess fluid on liver injury and metabolic acidosis during laparoscopic sleeve gastrectomy. Additionally, we could not evaluate liver tissue samples, a more direct indicator of liver injury than serum aminotransferases. Furthermore, determination of tissue levels of free oxygen radicals and nitric oxide synthase would advise the mechanism of hepatic injury during sleeve gastrectomy and probable preventive role of NAC. Nevertheless, this pilot study is one of the few studies in literature on the potential preventive role of NAC and excess fluid on liver injury during laparoscopic sleeve gastrectomy. On the basis of current findings, furthter large-scale, comparative studies should be conducted to conclude on the preventive role of intraoperative NAC and excess fluid application on liver injury and metabolic acidosis during laparoscopic sleeve gastrectomy. In conclusion, intraoperative infusion of 30 mg/kg NAC and 50 mL/kg fluid during laparoscopic sleeve gastrectomy may reduce liver injury and prevent metabolic acidosis, thus should be considered during surgical management of morbidly obese patients.

Conflict of interest disclosure

Authors declare no conflicts of interest.

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