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Original Research Article

A comparative study of intra-peritoneal instillation of lignocaine versus placebo on operative site in laparoscopic cholecystectomy

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ABSTRACT

Background: Visceral nociception is a significant source of the post-operative morbidity in Laparoscopic cholecystectomy and thus the idea of intraperitoneal local anaesthetic (IPLA) instillation was promulgated. The aim of the study was to evaluate the role of intra-peritoneal lignocaine instillation on post-operative morbidity in terms of post-operative pain and post-operative nausea and vomiting and also to establish if there is any difference exists between the timing of instillation of intra-peritoneal lignocaine (before and after completing the gall bladder dissection).
Methods: Eighty patients randomized into two groups lignocaine group (lignocaine instilled in gallbladder bed) and placebo group (saline instilled in gallbladder bed). Lignocaine group further divided into subgroups i.e. pre-dissection lignocaine group (lignocaine instilled before gallbladder dissection) and post-dissection lignocaine group (lignocaine instilled after gallbladder dissection).
Results: Post-operative pain was measured in terms of the VAS score. The score was less in lignocaine group. The difference was statistically significant ($p<0.05$) at 1, 2, 4, 6, 12 and 24hours between lignocaine group and placebo Group. No statistically significant difference between the mean of VAS scores of pre-dissections lignocaine and post-dissection lignocaine subgroups. In lignocaine group, 27.8%, 75%, 41% and 25% of the subject required rescue analgesia in 1st hr, next 1-8 hr, 8-16 hr and 16-24 hr respectively. In placebo group 33.3%, 97.2%, 83.3 % and 63.9% of the subject required rescue analgesia in 1st hr, next 1-8 hr, 8-16 hr and 16-24hr respectively. The difference was found to be statistically significant ($p<0.05$) except at 1st hour. Post operatively nausea perception, seemed to be slightly higher in placebo group as compared to lignocaine group but difference was statistically insignificant ($p>0.05$).
Conclusions: Intraperitoneal lignocaine instillation is an effective method to alleviate post-operative pain in patients undergoing laparoscopic cholecystectomy, whether used as pre-emptive analgesia or instilled at the end of surgery. Intraperitoneal lignocaine instillation decreases post-operative analgesia requirement, especially after the 1st post-operative hour.

Keywords: Intraperitoneal local anaesthetic, Laparoscopic cholecystectomy

INTRODUCTION

Laparoscopic cholecystectomy is known to be associated with considerable postoperative pain.[1] Alleviation of postoperative pain can be attempted by using battery of pharmacological agents ranging from NSAIDs to steroids to narcotics. Nevertheless, this attempt is often frustrating in case of postoperative nausea and vomiting. This has aptly been described as the "big little problem" by Kapur in an editorial review.[2]

For better management of postoperative pain, nausea and vomiting, it is important to appreciate the physiological process involved in pain initiation, propagation and response. There are visceral and somatic components of pain, further compounded by CO_2 used for peritoneal insufflation. Post-operative nausea-vomiting and pain constitute a vicious cycle which may aggravate each other. This concept of 'visceral nociception' as a significant source of post-operative morbidity needs to be addressed to further improve patient's experience after laparoscopic cholecystectomy.

In order to address the issue of 'visceral nociception' as a significant source of these post-operative morbidity, the idea of intraperitoneal local anesthetic (IPLA) instillation was promulgated. Thus, as the search for improving post-operative outcomes continues, this study was designed and conducted with a humble attempt to evaluate the efficacy of intra-peritoneal lignocaine instillation, and its timing, as an adjunct to reduce post-operative morbidities.

METHODS

Patients

The minimum required sample size was calculated using data of previous study conducted by Razek et al, applied in sample size calculator of Medcalc software (sample size calculation: comparing mean of groups).[3]

Table 1: Sample comparison of means of previous study.

Errors	Mean
Type I error (alpha, significance)	0.05
Type II error (Beta, 1-power)	0.20
Data	
Difference of means	14
Standard deviation in group 1	12.5
Standard deviation in group 2	18.8
Result	
Total sample size	42

Table 2: Sample size.

Table		Type I error			
		0.20	0.10	0.05	0.01
Type II error beta	0.20	13+13=26	17+17=34	21+21=42	32+32=64
	0.10	18+18=36	23+23=46	28+28=56	40+40=80
	0.05	23+23=46	29+29=58	35+35=70	48+48=96
	0.01	35+35=70	42+42=84	49+49=98	64+64=128

Table 3: Comparison of demographic profile of lignocaine and placebo group.

	Lignocaine group	Placebo group	P value
Age (yrs)	39.97	37.58	>0.05(t-test)
Gender (M:F)	1:3.5	1:8	>0.05(χ^2-test)
BMI(kg/m^2)	23.48	23.56	>0.05(t-test)
HTN	8 (22.2%)	6 (16.7%)	>0.05(χ^2-test)
DM	1 (2.8%)	2 (5.6%)	>0.05(χ^2-test)

Table 4: Comparison of demographic profile of pre-dissection lignocaine and post-dissection lignocaine group.

	Pre-dissection lignocaine group	Post-dissection lignocaine group	P value
Age(yrs)	40.86	39.25	>0.05(t-test)
Gender(M:F)	1:4.3	1:3	>0.05(χ^2-test)
BMI(kg/m^2)	22.78	24.03	>0.05(t-test)
HTN	3 (18.8%)	5 (25%)	>0.05(χ^2-test)
DM	1 (6.3%)	0 (0 %)	>0.05(χ^2-test)

Table 5: Comparison of operative parameters of lignocaine and placebo group.

		Lignocaine group	Placebo group	P value
No. of ports	4	27 (75%)	30 (83.3%)	>0.05(χ^2-test)
	3	9 (25%)	6 (16.7%)	
Adhesions		13(36.1%)	14(38.9%)	>0.05(χ^2-test)
Bile spillage		9(25%)	8(22.2%)	>0.05(χ^2-test)
Mean duration of surgery (mins)		46.9	42.1	>0.05(t-test)
Port site LA infiltration		36(100%)	36(100%)	NA

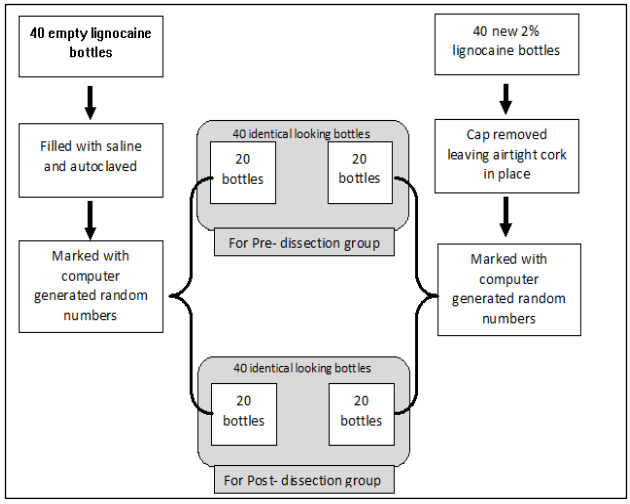

Figure 1: Flow chart depicting blinding method used.

Randomization and double blinding

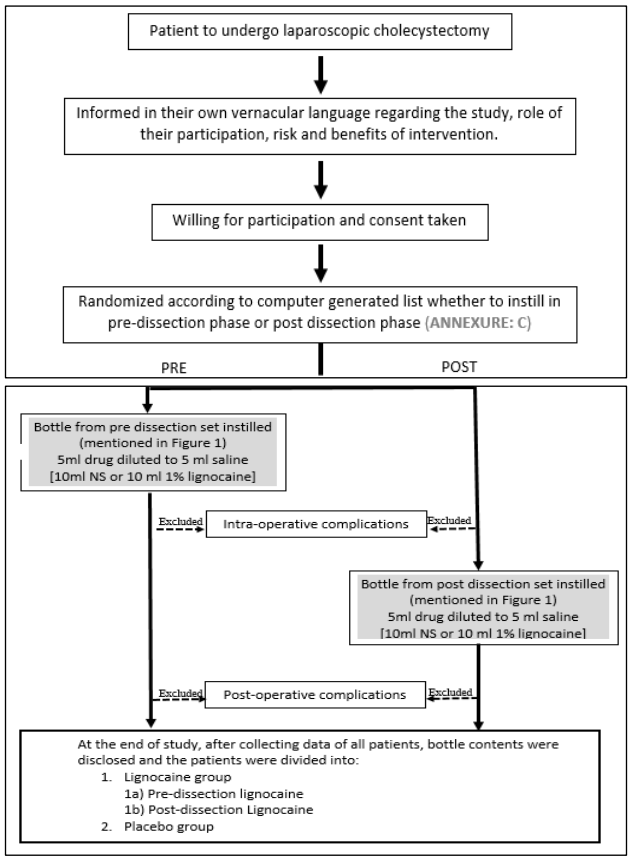

Figure 2: Flow chart depicting patient selection, exclusion, randomization and grouping.

Numbers allotted to bottles were computer generated password protected random numbers. These were marked by third person and the content of bottles were disclosed only at the end of the study after all data collection had completed. These two sets of bottles (40 each) were kept in two separate autoclaved drums. A computer generated random list of pre/post was created (40 each). Patients were instilled according to the list and bottles were picked from pre-dissection set and post-dissection set accordingly without having knowledge regarding the content of the vial.

Distribution of patients in the groups in terms of Age, Gender, BMI, Co-morbidity (DM and HTN) was not significantly different. Distribution of operative parameters of the patients in the groups in terms of adhesion, bile spillage, mean duration of surgery and no of ports were not significantly different.

Data recording

Drug instillation

- Code labelled bottle.
- Contents of the bottle were revealed by decoding after completion of study and collection of all data

Intra-operative parameters

Adhesions, bile or stone spillage, any injury to extra hepatic biliary system including the arteries and veins and any injury to regional arteries and vein.

Post-operative parameters (at 1, 2, 4, 6, 12 and 24hours)

- Pain (VAS Scale)
- Nausea-Vomiting
- Pulse Rate, Blood Pressure, Respiratory Rate
- Rescue analgesia
- Day of discharge

Statistical analysis

The relation between qualitative variables was assessed by chi square test. Student t-test was used for difference between means of different data arrays paired or unpaired two-tailed Student's t-test was employed, depending on the circumstance. ANOVA test was used to compare three or more means was used to compare percentage of paired data. The quantitative variables were summarized as mean and 95% Confidence Interval (CI).

RESULTS

Pain

Post-operative pain was measured in terms of the VAS score. The score was less in lignocaine group. The difference was statistically significant ($p<0.05$) at 1 hr, 2hr, 4 hr, 6 hr, 12 hr and 24 hr between lignocaine group and placebo Group. On the other hand, there was no statistically significant difference between the mean of VAS scores of pre-dissections lignocaine and post-dissection lignocaine subgroups.

Table 6: Comparison of VAS score between lignocaine (pre-dissection versus post-dissection) and placebo group.

Groups		1 hr		2 hr		4 hr		6 hr		12 hr		24 hr	
Lignocaine	Pre-dissection	3.36	4.06	4.31	4.13	3.97	3.88	3.94	3.81	3.06	2.63	2.28	1.94
	Post dissection		2.80		4.45		4.05		4.05		3.40		2.55
Placebo		5.86		6.67		5.72		5.22		4.61		3.72	

Table 7: P-value of t-test used in comparison of VAS score between the groups.

P value(t-test)	1 hr	2 hr	4 hr	6 hr	12 hr	24 hr
Lignocaine versus placebo	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Pre-dissection lignocaine versus Post-dissection lignocaine	0.120	0.672	0.776	0.651	0.128	0.275

Table 8: Mean of VAS score at various times post-operative pain in various age groups.

Age groups (years)	Whole sample	Lignocaine	Placebo	P value (χ^2-test)
10-20	6.22	--	6.22	NA
21-30	4.66	3.86	5.91	0.002
31-40	4.85	4.20	5.34	0.099
41-50	4.43	3.36	5.07	0.036
51-60	3.27	2.33	4.67	0.011
61-70	4.21	4.92	3.50	0.474
71-80	1.17	1.17	--	NA

Table 9: Comparison of VAS score between patient having adhesions to adhesion free.

		VAS(1hr)	VAS(2hr)	VAS(4hr)	VAS(6hr)	VAS(12hr)	VAS(24hr)
Whole sample	Adhesions	3.7	4.6	4.4	4.4	3.6	2.8
	No adhesions	5.1	6.0	5.1	4.7	4.0	3.1
	P (t-test)	0.035	0.008	0.120	0.385	0.322	0.529
Adhesions	Lignocaine	2.5	3.2	3.5	3.6	2.5	1.6
	Placebo	4.8	5.8	5.1	5.1	4.6	3.9
	P (t-test)	0.022	0.002	0.053	0.040	0.003	0.001
No adhesions	Lignocaine	3.8	4.9	4.2	4.1	3.4	2.7
	Placebo	6.5	7.2	6.1	5.3	4.6	3.6
	P (t-test)	0.001	<0.001	<0.001	0.004	0.016	0.104

Although the post-operative pain perception was significantly higher in females as compared to males, females seems to benefit more than males by intraperitoneal lignocaine instillation. Difference was not statistically significant. In context with age, pain perception showed declining trend with advancing age in both the groups.

Patients having intra-operative adhesion seems to have lesser post-operative pain in both the groups. On the other hand, no relation could be established with other factors like bile spillage, stone spillage and duration of surgery.

Post-operative analgesia

In lignocaine group, 27.8%, 75%, 41% and 25% of the subject required rescue analgesia in 1sthr, next 1-8 hr, 8-16 hr and 16-24 hr respectively. In placebo group 33.3%, 97.2%, 83.3 % and 63.9% of the subject required rescue analgesia in 1st hr, next 1-8 hr, 8-16 hr and 16-24 hr respectively. The difference was found to be statistically significant ($p<0.05$) except at 1st hour. The difference in post-operative analgesia required in pre-dissection lignocaine and post-dissection lignocaine group was statistically insignificant ($p >0.05$).

Post-operative nausea and vomiting

Post operatively nausea perception, seemed to be slightly higher in placebo group as compared to lignocaine group but difference was statistically insignificant ($p>0.05$). Incidence of post-operative nausea was negligible after 4th post-operative hour. There was no significant difference ($p >0.05$) in post-operative vomiting between

placebo and lignocaine group. The subgroup statistical analysis showed similar results.

Post-operative vitals

Post-operative pulse rate was lower in the patients receiving intraperitoneal lignocaine instillation as compare to patients of placebo group It was significantly different ($p<0.05$) at 1st hr and 12th hr between lignocaine group and placebo group. The subgroups pre-dissection lignocaine and post-dissection lignocaine, showed no statistically significant difference in post-operative pulse rate ($p>0.05$). However other parameters including mean arterial pressure, respiratory rate and SpO_2 were similar in both groups.

Adverse events

No adverse reaction to lignocaine has been reported in any of the patients included in the study.

Day of discharge

Patients of lignocaine group had significantly shorter duration of hospital stay as compared to placebo group. While no difference observed between the subgroups; pre-dissection lignocaine and post dissection lignocaine group ($p >0.05$).

Table 10: Comparison of incidence of post-operative analgesia required in lignocaine (pre-dissection versus post-dissection) and placebo group.

		Rescue analgesia 1hr		Rescue analgesia in next 1-8 hr		Rescue analgesia in next 8-16 hr		Rescue analgesia in next 16-24 hr	
Lignocaine	Pre	27.8%	31.3%	75.0%	68.75%	41.7%	43.75%	25.0%	25%
	Post		25.0%		80%		40%		25%
Placebo		33.3%		97.2%		83.3%		63.9%	

Table 11: P-value of $\chi 2$ -test used in comparing incidence of post-operative analgesia required in lignocaine (pre-dissection versus post-dissection) and placebo group.

P value(χ^2-test)	Rescue analgesia 1hr	Rescue analgesia in next 1-8 hr	Rescue analgesia in next 8-16 hr	Rescue analgesia in next 16-24 hr
Placebo versus lignocaine	0.609	0.006	<0.001	<0.001
Pre-dissection lignocaine versus Post-dissection lignocaine	0.677	0.439	0.821	1

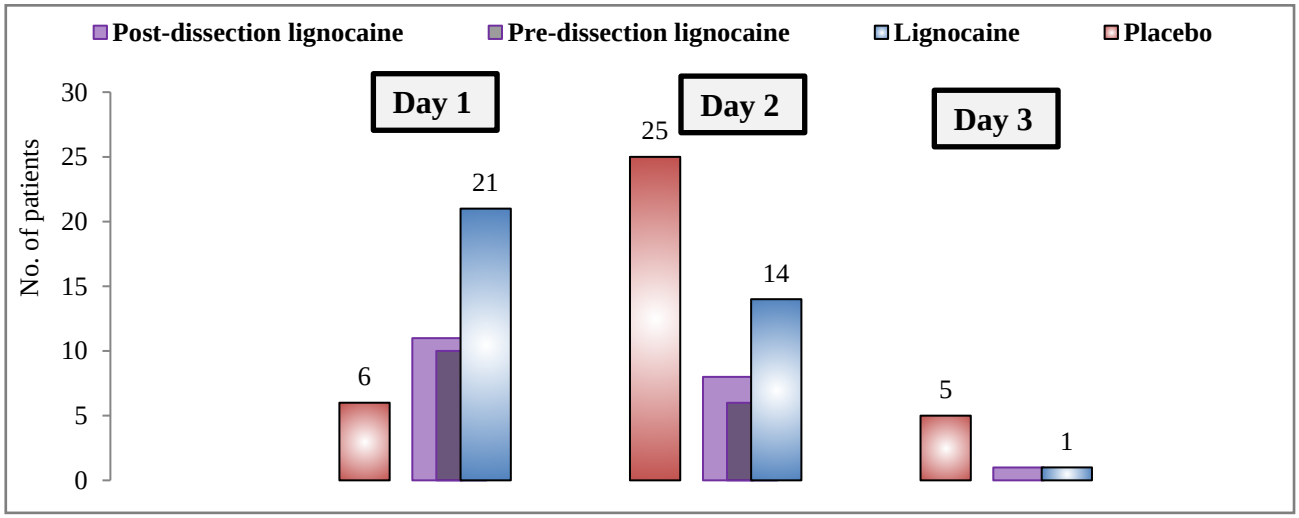

Figure 3: Comparison of day of discharge between various groups.

DISCUSSION

The pain after laparoscopic cholecystectomy is multi-factorial and can be because of the one arising from incision sites (somatic pain), from the gallbladder bed (visceral pain) and as a consequence of capnoperitoneum. It is therefore likely that combined methods of analgesia can best reduce the post-operative pain.[4] Four main types of visceral stimuli (electrical, mechanical, ischemic and chemical) have been employed in experimental studies on visceral nociception.[5]

The available evidence indicates that these two classes of visceral extrinsic nerves (vagal and spinal) exhibit a number of contrasting properties, which in turn reflect their diverse role in sensory signaling. An enormous range of chemical mediators have been implicated in sensory signal transduction in the viscera.

Local anesthetics directly interact with voltage-gated Na^+ channels and block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane.[6]

Considering the important role of sodium channels in pain pathway and the effectiveness of local anaesthesia in blocking them, it's obvious that local anaesthesia can be utilized to alleviate post-operative pain. Direct application of local anaesthesia to the site of surgical dissection seems a prudent appropriate in this respect.

LAs have well known anti-inflammatory actions. Animal work on IPLA has been interesting and showed lignocaine and bupivacaine prevented peritonitis and adhesion formation. Eutectic mixture of local anaesthetics (EMLA-lignocaine/procaine) inhibited the adhesion formation after bacterial peritonitis in rats compared with controls.[7,8] Lignocaine applied to obstructed bowel serosa, inhibited and reversed gut fluid losses and inflammation.[9] To the knowledge, these benefits have not been shown clinically.

The mechanism of action of IPLA is not fully understood, although it is likely that there is blockade of free afferent nerve endings in the peritoneum. Systemic absorption of LA from the peritoneal cavity may also play some part in reduced nociception.

The peritoneum cavity is the largest serous membrane in the body and has a surface area of $1.8m^2$, close to that of the skin.[10] It is known that systemic levels of LA are detectable in the serum circulation as soon as 2 minutes after bolus instillation into the peritoneum, reaching a systemic maximum after 10-30 min.[11]

Table 12: Comparison of postoperative pain in laparoscopic cholecystectomy from various research study.

Study	Significant difference	Post-operative (hour)
Current study	Yes	1^{st}, 2^{nd}, 4^{th},6^{th},12^{th}, 24^{th}
Memedov C et al.[12]	Yes	2^{nd}, 4^{th}, 8^{th}, 12^{th}, 18^{th}, 24^{th}
Goluboviv S et al.[13]	Yes	0.5, 1^{st}, 2^{nd}, 4^{th}, 6^{th}
Boddy AP et al.[18]	Yes	4^{th} hr
Bhardwaj N et al.[14]	Yes	1^{st}, 4^{th}, and 8^{th}
Roberts KJ et al.[15]	No	-
El-laban GM et al.[16]	No	--
Lepner U et al.[17]	No	--

In Present study pain was higher in placebo group then the treatment group and was statistically significant at each hour. Similar findings were confirmed in other studies while some study found no beneficial effect of intraperitoneal local anesthetic instillation in relieving post-operative pain.[12-17]

CONCLUSION

Intraperitoneal lignocaine instillation is an effective method to alleviate post-operative pain in patients undergoing laparoscopic cholecystectomy, whether used as pre-emptive analgesia or instilled at the end of surgery.

Intraperitoneal lignocaine instillation decreases post-operative analgesia requirement, especially after the 1st post-operative hour. Females are more likely to benefit from intraperitoneal lignocaine instillation with respect to post-operative pain, as compared to males. Intraperitoneal lignocaine instillation may decrease the incidence of post-operative nausea vomiting. Duration of hospital stay is less in patients receiving intraperitoneal lignocaine instillation.

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