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Original article

Ultrasound guided Transverses Abdominis Plane block using bupivacaine with or without hyaluronidase in laparoscopic cholecystectomy

Rania Abd El-Halim Sherif[a], Mohamed Fawzi Abd El-Nabi[a], Mahmoud Attia Ali[a], Ahmed Mostafa El-Shaarawy[a]

[a] *Anesthesiology, surgical intensive care and pain management, Beni-Suef University Hospital, Beni-Suef University, Egypt.*

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Corresponding Author:

Mohamed Fawzi Abd El-Nabi

thezedoooo@gmail.com

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Abstract

Aim: The purpose of this study is to compare the efficacy of of Bupivacaine 0.25% alone versus the Bupivacaine 0.25% with Hyaluronidase 1500 I.U during ultrasound guided transversus abdominis plane block in elective laparoscopic cholecystectomy under general anesthesia. **Patients and methods:** This Randomized Controlled-double-blind study was conducted on 60 Patients randomized into two groups. Group A (30 patients), TAP block was performed using Bupivacaine 0.25% 20 ml on each side of abdominal wall. Group B (30 patients), TAP block was performed using a combination of 18 ml of Bupivacaine 0.25% and 2 ml of Hyaluronidase 750 I.U on each side of abdominal wall. This study was carried out in the department of Anesthesiology, surgical intensive care and pain management in Beni-Suef University hospital. **Results:** Regarding the total analgesic amount requirements, this study showed that there was no statistically significant difference between both groups regarding the dose of analgesia after 2, 4, 6, 12, 16, 20, and 24

postoperatively. There was a statistically significant longer mean time to 1st request of analgesia being 10.2±3.1 hours in bupivacaine and hyaluronidase group than bupivacaine only group being 5.2±1.9 hours. According to the NSR pain score, there was no statistically significant difference between bupivacaine and hyaluronidase group and bupivacaine only group after 2, 4, 6, 8, 12, 16, 20, and 24 of the operation. **Conclusion:** Using hyaluronidase as an adjuvant to bupivacaine in sonar-guided TAP block after laparoscopic cholecystectomy offered good postoperative analgesia, postponed the need for analgesia, and decreased analgesic intake early postoperatively.

1. Introduction:

A minimally invasive technique called laparoscopic cholecystectomy results in moderate levels of visceral, parietal, referred, and incisional postoperative pain (1).

The transversus abdominis plane (TAP) block is a technical approach of regional anesthesia that lessens the discomfort associated with abdominal wall incisions, reduces the need for general anesthesia, improves hemodynamic stability, and is a safe and effective part of postoperative pain management. It also lengthens the interval before the patient first requests narcotics, which lowers narcotic consumption overall (2,3).

An enzyme known as hyaluronidase is regarded as the "spreading factor," making local anesthetic solutions easier to disperse. It has been demonstrated to cause reliable blockade with better spread and hence improved grade of block when used with local anesthetics (4).

If accidentally supplied intravenously, bupivacaine is the most cardiotoxic and longest acting local anesthetic. Since its debut, it has been used successfully and has come to be the standard by which all other long-acting local anesthetics are measured. It's interesting to note that bupivacaine tends to cause sensory blocks at low concentrations while only somewhat sparing the motor blocks (differential sensitivity) (5).

The purpose of this study is to compare the efficacy of Injection of Bupivacaine 0.25% and Injection of Bupivacaine 0.25% with

Hyaluronidase 1500 I.U ultrasound guided transversus abdominis plane block in elective laparoscopic cholecystectomy surgeries performed under general anesthesia with respect to quality of analgesia, time to peak analgesia and duration of post-operative analgesia and need for rescue analgesic, reduction in 24-hour intravenous opioid and consumption and adverse effects if any.

2. Patients and methods:

Type of study:

This study is Randomized-Controlled double-blind study.

Sample Size:

The sample size was calculated by G power program with assumption of difference between two independent means with effect size 0.9 and alpha error 0.05, the sample size was 30 in each group.

Site of study:

This research was conducted at Beni-Suef University Hospital with the permissions of the hospital's local ethics committee and the anesthesia, critical care, and pain management departments.

Duration of the study:

6 months (from July 2021 to January 2022)**.**

Randomization and Blinding (Double blind comparative study)

The patients were allocated randomly using sealed opaque numbered envelopes into two equal groups; carried out by an anesthesiologist who was blinded to the study groups.

- Group A: Received TAP block with Bupivacaine 0.25% 20 ml on each side of abdominal wall
- Group B: Received TAP block with Bupivacaine 0.25% 18 ml + Hyaluronidase 750 I.U (dissolved in 2 ml Bupivacaine) on each side of abdominal wall

In the same syringes, the study solutions were made. The study protocol was hidden from the anesthesia residents who administered the study drug, handled general anesthesia, and were in charge of data collection.

Inclusion criteria:

Subjects with American Society of Anesthesiology physical status (ASA) I & II of both sexes, age between 18 and 60 years and were scheduled for elective laparoscopic cholecystectomy surgery under general anesthesia were included in this study.

Exclusion criteria:

Patients refused to assign consent, with history of allergy to hyaluronidase or bupivacaine, with significant respiratory, cardiac or systemic diseases, on analgesics in the past 24 hours, and with any contraindication to peripheral nerve blocking

e.g. (coagulopathy, infection at the injection site) were excluded from the study.

The primary outcome:

Total analgesic amount requirements.

The secondary outcomes:

Post-operative pain evaluation and time to first request of analgesia.

Methods:

Preoperative evaluation for all patients was done including full history, routine investigations and proper physical examination. Only ASA I and II patients were enrolled in the study. General anesthesia was induced using fentanyl 1-2 µg/kg IV and propofol 2-2.5 mg/kg IV and endotracheal intubation was facilitated with atracurium 0.5 mg/kg IV. Maintenance of anesthesia with isoflurane 1.2% in a 40:60 mixture of oxygen and air.

A tidal volume and rate adjustment was made to start positive pressure breathing while maintaining an end-tidal PCO2 of 30 to 40 mmHg.

Baseline heart rate, oxygen saturation (SpO2), noninvasive blood pressure, continuous electrocardiography, end-tidal carbon dioxide, and temperature were all measured in all patients. At the end of surgery and residual neuromuscular blockade were reversed with IV neostigmine 50 µg/kg and IV atropine 10 µg/ kg. All patients received IV ondansetron 0.1 mg/kg prior to completion of the surgery. An oblique subcostal route was used to give the US guided TAP block before extubation at the conclusion of operation. The ultrasonography was from Philips (Model: HD5 , S/N: CI56150284 , Washington USA 2015). The abdominal wall's skin on both sides was disinfected with a solution of 70% isopropyl alcohol while the patient was supine. High frequency linear array transducer (5-12 MHz) was positioned inferiorly and parallel to costal margin in mediolateral orientation while in sterile conditions. At the midaxillary line, the muscles of the external, internal, and transverse obliques were found. A 18G, short bevel echogenic needle was inserted medially and in plane to the US beam until the tip lied between the fascia of internal oblique and transversus abdominis muscle layers where injecting 20 ml of study drug on each side of abdominal wall under direct visualization. Following the completion of surgery, patients were transferred to postoperative anesthesia care unit (PACU) for monitoring for the first time and then observed regularly every 2 hours for 24 hours postoperatively

Assessment parameters and follow up:

Postoperative hemodynamic variables as blood pressure, heart rate and SPO2 were assessed in PACU immediately after

patient's arrival and then assessed regularly every 2 hours for 24 hours postoperatively. NRS (numeric rating scale) a pain scoring system was used by the patient, the patient put a mark on a horizontal line which reads "no pain at all" at one end 0 end, and "worst pain imaginable" at the other end at 10 **(6).** Dosing of IV analgesics was based on pain intensity as assessed using the numeric rating scale. If the patient reported NRS scores > 4, a dose of nalbuphine 4mg I.V. was given as rescue analgesia and repeat as needed during the first 24 hours postoperatively and the total amount of analgesic requirements per day were calculated. Side effects, such as hypotension, bradycardia, allergic reaction if any, nausea or vomiting.

Statistical Data Analysis:

Nominal variables were reported as a number or percentage and compared across groups using the relevant Fisher's exact test or Pearson's Chi-square test for attribute independence. The Mann-Whitney U-test was used to compare continuous variables across groups after they had been reported as mean and standard deviation. Follow up changes of scale parameters were tested by repeated measure ANOVA. The statistical software SPSS version 25 (IBM) was used for the analysis. An alpha level of 5% has been taken, i.e., if any $P < 0.05$, it was considered as significant.

Ethical Considerations:

The study was approved by the local research and ethical committee with a number (FMBSUREC/07092021/ Abd El-Nabi) and a written informed consent was obtained from each patient before the operation.

3. Results:

Patients randomly assigned into 2 equal groups:

Group I: Bupivacaine only group (no=30).

Group II: Bupivacaine and hyaluronidase group (no=30).

Table (1) showed that there was no statistically significant difference between bupivacaine only group and bupivacaine and hyaluronidase group regarding their baseline characteristics as age, sex, and ASA.

Table (1) Baseline characteristics of the studied groups:

Characteristics	Group I (no=30)	Group II (no=30)	P-value
Age (mean±SD)	38.8±8.2	41±8.3	0.301
Sex **Males** **Females**	 8(26.7%) 22(73.3%)	 13(43.3%) 17(56.7%)	0.176
ASA	1.2±0.4	1.2±0.4	>0.999
ASA categories **I** **II**	 25(83.3%) 5(16.7%)	 25(83.3%) 5(16.7%)	>0.999

There was a statistically significant higher systolic blood pressure in bupivacaine and hyaluronidase group than bupivacaine only group after 2, 4, 6, 8, 12 and 24 hours of the operation but the percentage of increase (from 2 hours to 24 hours) was significantly higher in bupivacaine only group than bupivacaine and hyaluronidase group (table (2).

Table (2) Comparison between both groups regarding systolic blood pressure (SBP) at different times among the studied groups:

SBP	Group I (no=30)	Group II (no=30)	P-value
After 2 hours	86.4±5.3	99.9±7	<0.001*
After 4 hours	100.6±6.4	111.3±3	<0.001*
After 6 hours	111±6.3	114.6±19.7	0.350
After 8 hours	116.4±6.2	124.6±2	<0.001*
After 12 hours	120.5±6.1	121.1±5.7	<0.001*
After 24 hours	131.6±4.3	134.1±2.1	0.007*
Percentage of increase (%)	52.8±9.9	34.9±10.9	<0.001*

SBP: systolic blood pressure **P-value is significant*

Table (3) showed that there was a statistically significant higher diastolic blood pressure in bupivacaine and hyaluronidase group than bupivacaine only group after 2, 4, 6, 8, 12 and 24 hours of the operation but the percentage of increase (from 2 hours to 24 hours) was significantly higher in bupivacaine only group than bupivacaine and hyaluronidase group.

Table (3) Comparison between both groups regarding diastolic blood pressure at different times among the studied groups:

DBP	Group I (no=30)	Group II (no=30)	P-value
After 2 hours	63.5±3.1	67.9±2.3	<0.001*
After 4 hours	68.8±2.7	73.3±2.1	<0.001*
After 6 hours	72.9±2.4	77.6±1.7	<0.001*
After 8 hours	77.6±1.7	82.4±1.6	<0.001*
After 12 hours	83.4±1.9	87.3±1.7	<0.001*
After 24 hours	84.2±3.2	87.9±2.4	<0.001*
Percentage of increase	32.7±4.1	29.6±3.1	0.002*

DBP: diastolic blood pressure **P-value is significant*

Table (4) showed that there was a statistically significant higher heart rate in bupivacaine and hyaluronidase group than bupivacaine only group after 2, 4, 6, 8, 12 and 24 hours of the operation but the percentage of increase (from 2 hours to 24 hours) was significantly higher in bupivacaine only group than bupivacaine and hyaluronidase group.

Table (4) Comparison between both groups regarding heart rate at different times among the studied groups:

HR	Group I (no=30)	Group II (no=30)	P-value
After 2 hours	66.2±2.7	70.7±3.3	<0.001*
After 4 hours	70.2±2.9	74.6±2.7	<0.001*
After 6 hours	74.8±2.4	82.3±2.3	<0.001*
After 8 hours	82.2±2.7	86.5±1.4	<0.001*
After 12 hours	86.4±1.3	87.2±1.5	<0.001*
After 24 hours	86.7±1.5	86.9±1.6	<0.001*
Percentage of increase	31.2±5.3	23.2±6.5	<0.001*

HR: Heart rate **P-value is significant*

There was a statistically significant lower oxygen saturation in bupivacaine and hyaluronidase group than bupivacaine only group after 8 and 12 of the operation but the percentage of increase (from 2 hours to 24 hours) was didn't differ significantly in both groups (table 5).

Table (5) Comparison between both groups regarding SpO_2 at different times among the studied groups:

SpO_2	Group I (no=30)	Group II (no=30)	P-value
After 2 hours	97.2±1.2	96.9±0.9	0.306
After 4 hours	97.2±1.2	96.9±0.9	0.306
After 6 hours	96.8±0.9	96.9±1.3	0.574
After 8 hours	98.2±0.8	97.5±0.8	<0.001*
After 12 hours	98±0.8	97.2±0.9	<0.001*
After 24 hours	97.8±0.8	97.9±1	0.782
Percentage of increase	0.6±1.5	1±1.7	0.363

SpO2: Spot Oxygen Saturation **P-value is significant*

Table (6) showed that there was no statistically significant difference between bupivacaine and hyaluronidase group and bupivacaine only group after 2, 4, 6, 8, 12, and 24 of the operation in addition to the percentage of increase (from 2 hours to 24 hours) that was didn't differ significantly in both groups.

Table (6) Comparison between both groups regarding NSR pain score at different times among the studied groups:

NSR	Group I (no=30)	Group II (no=30)	P-value
After 2 hours	3.3±2	3.2±1.8	0.844
After 4 hours	3.1±2	2.7±2	0.447
After 6 hours	2.9±1.8	2.5±1.5	0.414
After 8 hours	2.8±1.9	3.2±2.1	0.381
After 12 hours	3.5±2.3	3.1±2.1	0.454
After 24 hours	3.4±2.4	2.5±1.7	0.096
Percentage of decrease	79.6±227.4 (median=70)	30.6±179 (median=29)	0.358

NSR pain: Numerical Rating Scale

Table (7) showed that there was a statistically significant longer mean time to 1st request of analgesia in bupivacaine and hyaluronidase group than bupivacaine only group but there was no statistically significant difference between both groups regarding the dose of analgesia after 2, 4, 6, 8, 12, and 24 of the operation in addition to the total amount of analgesia.

Table (7) Comparison between both groups regarding analgesia dose and time to 1st requirement among the studied groups:

Nalbuphine dose (mg)	Group I (no=30)	Group II (no=30)	P-value
Time to 1st request of analgesia (hrs)	5.2±1.9	10.2±3.1	<0.001*
After 2 hours	0.9±1.7	0.7±1.5	0.527
After 4 hours	0.8±2.2	0.5±1.7	0.605
After 6 hours	0.4±1.6	0.1±0.7	0.412
After 8 hours	1.1±2.7	1.3±3	0.723
After 12 hours	2.4±3.7	1.6±3.2	0.380
After 24 hours	1.7±3.5	0.7±2.5	0.192
Total amount of analgesia (mg)	9.2±8.2	6.3±6.9	0.141

**P-value is significant*

Table (8) showed that there was no statistically significant difference between both groups regarding the post operative side effects.

Table (8) Comparison between both groups regarding the occurrence of side effects:

SE	Group I (no=30)	Group II (no=30)	P-value
Hypotension	6(20.0%)	2(6.7%)	0.254 (FET)
Bradycardia	0(0%)	0(0%)	------
Nausea	8(26.7%)	6(20.0%)	0.542
Vomiting	0(0%)	0(0%)	---------
Pruritis	0(0%)	0(0%)	------

SE: Side effects FET: Fisher's exact test

Table (9) showed that were a significant increase of systolic, diastolic and heart rate from 2 hours till 24 postoperatively in bupivacaine only group.

Table (9) Follow up changes of systolic, diastolic blood pressure and heart rate in bupivacaine only group:

Bupivacaine only group		Mean	Std. Deviation	P-value
Systolic blood pressure	**Sys. BP 2 hours**	86.4333	5.30896	<0.001*
	Sys. BP 4 hours	100.600	6.35501	
	Sys. BP 6 hours	111.033	6.34895	<0.001*
	Sys. BP 8 hours	116.433	6.17382	
	Sys. BP 12 hours	121.100	5.66508	<0.001*
	Sys. BP 24 hours	131.633	4.33497	
Diastolic blood pressure	**Dia. BP 2 hours**	63.5000	3.12664	<0.001*
	Dia. BP 4 hours	68.8000	2.69610	
	Dia. BP 6 hours	72.9667	2.37056	<0.001*
	Dia. BP 8 hours	77.6333	1.79046	
	Dia. BP 12 hours	83.3667	1.95613	0.051
	Dia. BP 24 hours	84.2000	3.19914	
Heart rate	**HR 2 hours**	66.1667	2.74281	<0.001*
	HR 4 hours	70.1667	2.99521	
	HR 6 hours	74.8333	2.40808	<0.001*
	HR 8 hours	82.2000	2.67040	
	HR 12 hours	86.4333	1.27802	0.472
	HR 24 hours	86.6667	1.49328	

**P-value is significant*

Table (10) showed that there was no statistically significant changes of oxygen saturation and pain score at different times during the 1st 24 hours except from 6 to 8 hours the oxygen saturation increased significantly from 96.8±0.96 to 98.2±0.8 in the bupivacaine only group.

Table (10) Follow up changes of oxygen saturation and pain score in bupivacaine only group:

Bupivacaine only group		Mean	Std. Deviation	P-value
SPO2	SPO2 (%) 2 hours	97.2000	1.24291	----------
	SPO2 (%) 4 hours	97.2000	1.24291	
	SPO2 (%) 6 hours	96.8000	.96132	<0.001*
	SPO2 (%) 8 hours	98.2333	.77385	
	SPO2 (%) 12 hours	98.0333	.80872	0.282
	SPO2 (%) 24 hours	97.8000	.84690	
NSR score	Pain (NSR) 2 hours	3.3333	2.03983	0.738
	Pain (NSR) 4 hours	3.1333	2.02967	
	Pain (NSR) 6 hours	2.8667	1.85199	0.455
	Pain (NSR) 8 hours	2.7667	1.97717	
	Pain (NSR) 12 hours	3.5000	2.28564	0.876
	Pain (NSR) 24 hours	3.4000	2.42970	

**P-value is significant*

Table (11) showed that were a significant increase of systolic, diastolic and heart rate from 2 hours till 24 postoperatively in Bupivacaine and hyaluronidase group but there was a steadiness of systolic blood pressure from 4 to 6 hours, diastolic from 12 to 24 hours and heart rate from 8 to 24 hours (P-value>0.05).

Table (11) Follow up changes of systolic, diastolic blood pressure and heart rate in Bupivacaine and hyaluronidase group:

Bupivacaine and hyaluronidase		Mean	Std. Deviation	P-value
Systolic blood pressure	Sys. BP 2 hours	99.900	7.04836	<0.001*
	Sys. BP 4 hours	111.266	3.00498	
	Sys. BP 6 hours	114.600	19.74073	0.010*
	Sys. BP 8 hours	124.600	2.04434	
	Sys. BP 12 hours	128.433	3.12590	<0.001*
	Sys. BP 24 hours	134.100	2.09021	
Diastolic blood pressure	Dia. BP 2 hours	67.900	2.30965	<0.001*
	Dia. BP 4 hours	73.2667	2.13240	
	Dia. BP 6 hours	77.6000	1.71404	<0.001*
	Dia. BP 8 hours	82.4333	1.59056	
	Dia. BP 12 hours	87.2667	1.65952	0.179
	Dia. BP 24 hours	87.9667	2.41380	
Heart rate	HR 2 hours	70.7333	3.32113	<0.001*
	HR 4 hours	74.5667	2.68692	
	HR 6 hours	82.3000	2.30666	<0.001*
	HR 8 hours	86.5000	1.35824	
	HR 12 hours	87.2333	1.47819	0.455
	HR 24 hours	86.9667	1.56433	

**P-value is significant*

Table (12) showed that there was no statistically significant changes of oxygen saturation and pain score at different times during the 1st 24 hours except from 12 to 24 hours the oxygen saturation increased significantly from 97.2±0.9 to 97.9±1 in the Bupivacaine and hyaluronidase group.

Table (12) Follow up changes of oxygen saturation and pain score in Bupivacaine and hyaluronidase group:

Bupivacaine and hyaluronidase group		Mean	Std. Deviation	P-value
SPO2	SPO2 (%) 2 hours	96.9000	.99481	------
	SPO2 (%) 4 hours	96.9000	.99481	
	SPO2 (%) 6 hours	96.9667	1.29943	.053
	SPO2 (%) 8 hours	97.4667	.81931	
	SPO2 (%) 12 hours	97.2000	.92476	.028*
	SPO2 (%) 24 hours	97.8667	1.00801	
NSR score	Pain (NSR) 2 hours	3.2333	1.86960	.280
	Pain (NSR) 4 hours	2.7333	2.01603	
	Pain (NSR) 6 hours	2.5000	1.59201	.517
	Pain (NSR) 8 hours	3.2333	2.11209	
	Pain (NSR) 12 hours	3.0667	2.16450	.746
	Pain (NSR) 24 hours	2.4667	1.79527	

**P-value is significant*

4. Discussion:

Postoperative pain control is a significant topic that has drawn a lot of interest from the medical community. For an early recovery, early mobility, early return to work, and a brief hospital stay, pain management is crucial. Laparoscopic surgeries have used a variety of techniques to reduce postoperative pain, including opioid use, non-steroidal anti-inflammatory drugs, local anesthetic injections at the sites of the incisions, pneumoperitoneum pressure reduction, nongaseous laparoscopy, and traumatized intra-abdominal lavage with saline (7).

After laparoscopic surgery, the multimodal analgesic strategy is generally recognized as a crucial part of an improved recovery program since it reduces postoperative problems, including pain. Blocking the transversus abdominis plane (TAP) is a dependable and repeatable analgesic technique. The effectiveness of

TAP block alone in relieving pain after laparoscopic cholecystectomy is limited (8).

This study was conducted at Beni-Suef University Hospital to compare the efficacy of injection of bupivacaine 0.25% and injection of bupivacaine 0.25% with hyaluronidase 1500 I.U ultrasound guided transversus abdominis plane block in elective laparoscopic cholecystectomy surgeries performed under general anesthesia.

The primary outcome of this study was the total analgesic amount requirements. This study showed that there was no statistically significant difference between both groups regarding the dose of analgesia after 2, 4, 6, 12, 16, 20, and 24 of the operation in addition to the total amount of analgesia. However, the average total amount of analgesia requested by patients in bupivacaine and hyaluronidase group was 6.3±6.9 still lower than that requested by patients in bupivacaine only group that was 9.2±8.2.

Similar results were reported by Marzouk *et al.*, (2020) who studied the effect of adding hyaluronidase to bupivacaine in US guided transversus abdominus plain block following bariatric surgeries. They reported that patients in the group of bupivacaine and hyaluronidase have a lower mean of opioid consumption in 2nd, 4th, 6th, 8th,16th, 22nd and 24th postsurgical day with overall lower mean of opioid consumption (9).

Blocks of the transversus abdominis plane (TAP) may be carried out both before and after surgery. During the first 24-48 hours postoperatively, the single-shot TAP blocks offer analgesia with a decrease in pain ratings and narcotic use (10).

The placement of local anesthetics in the transversus abdominis fascial plane, which may result in sensory block along the anterior abdominal wall from T7 to L1, may explain the significance of TAP block in postoperative analgesia after abdominal surgery (11).

Because the TAP is generally minimally vascularized, drug clearance may be hindered, which may be one of the causes of the longer persistence of the analgesic action following TAP blocking (12).

In nerve blocks, using hyaluronidase as an adjuvant to the local anesthetics may be very important. It has been suggested that the mucolytic enzyme hyaluronidase, which works on the mucopolysaccharide hyaluronic acid, is a spreading factor (13).

The effect of hyaluronidase in reducing tissue resistance is much greater than might be anticipated, which may be because it hydrolyzes both hyaluronic acid and chondroitin sulfate, another component

of ground substance. This may aid in the widespread distribution of the drugs in the tissue planes even though hyaluronic acid only makes up 2% of the total tissue flow resistance (14).

In contrary to our study is that performed by Hakim and Ahmed, (2017) who concluded that although the use of hyaluronidase as an adjuvant to the local anaesthetic had a little effect on the total analgesic duration and on the consumption of postoperative analgesics after the ultrasound-guided supraclavicular brachial plexus block (15).

Also, Hyaluronidase was introduced to ropivacaine in an axillary brachial plexus block by Koh et al. (2015). The amount of opioids consumed intraoperatively and postoperatively did not, however, significantly vary from one another. Such results that vary from those of the current research may be attributable to various anesthetic drugs, doses, and anesthetic procedures (16).

The secondary outcomes of this study were the post-operative pain evaluation using the NSR pain score and time to first request of analgesia. There was a statistically significant longer mean time to 1st request of analgesia being 10.2±3.1 hours in bupivacaine and hyaluronidase group than bupivacaine only group being 5.2±1.9 hours. According to the NSR pain score, there was no statistically significant difference between bupivacaine and hyaluronidase group and bupivacaine only group after 2, 4, 6, 8, 12, 16, 20, and 24 of the operation. In both groups, the NSR pain score decreased gradually after the operation till 8 hours reaching average of 2.3±1.1 in bupivacaine and hyaluronidase group and 2.5±1.6 in bupivacaine only group. Then, the NSR pain score increased again from 8 hours to 24 hours. In addition to the percentage of increase (from 2 hours to 24 hours) that didn't differ significantly in both groups.

These results match with that reported by Compared to patients in the bupivacaine alone group, patients in the bupivacaine plus hyaluronidase group had considerably reduced mean VAS ratings postoperatively, according to Petkar et al (2020)'s research (17).

Also, in the same line is the study of Petkar *et al.,* (2020) about the effect of hyaluronidase as adjuvant in ultrasound-guided TAP block in total abdominal hysterectomy. They revealed that the mean time of demand for the analgesia in bupivacaine and hyaluronidase group was 351.32 ± 15.97 min as compared to bupivacaine only group which was 307.76 ±

13.19 min. The cumulative dose of rescue analgesic injection fentanyl needed was more in bupivacaine only group as compared to bupivacaine and hyaluronidase group (17).

Additionally, Chaudhari and Chaudhari (2013) discovered that the hyaluronidase group's mean duration of analgesia was statistically significant longer and had lower pain levels at 2 and 6 hours. They found that hyaluronidase with local anesthetic prolongs postoperative analgesia and provide good intraoperative analgesia for inguinal hernia block (18).

Also, Abdelaziz and Abd Elghany, (2021) reported similar results in their study, they found that adding hyaluronidase to bupivacaine in rectus sheath block significantly reduced the degree of postoperative pain shown by lower pain scores NRS in bupivacaine and hyaluronidase group at 0, 1, 2, 4 and 6 hours postoperatively than in bupivacaine only group (19).

Similarly, In a research by Mittal et al. (2018), patients having laparoscopic sleeve gastrectomy were compared to those receiving no postoperative ultrasound-guided TAP block. Patients in the TAP block group had less pain during the first 48 hours and needed fewer doses of rescue drugs overall (20).

Also, the trial of Ruiz-Tovar *et al.*, (2018) on patients having laparoscopic gastric bypass, a comparison of laparoscopic TAP block to infiltration at the trocar site was carried out. Much fewer patients in the TAP group required morphine within the first 24 hours, and their pain levels were significantly lower (21).

Regarding the hemodynamics of the patients under the study, there was a statistically significant higher systolic and diastolic blood pressure in bupivacaine and hyaluronidase group than bupivacaine only group after 2, 4, 6, 12, 18 and 24 hours of the operation but the percentage of increase (from 2 hours to 24 hours) was significantly higher in bupivacaine only group than bupivacaine and hyaluronidase group. However, the highest mean systolic blood pressure was after 24 hours in bupivacaine and hyaluronidase group and reached 134.1±2.1. Also, the highest mean diastolic blood pressure was after 24 hours in bupivacaine and hyaluronidase group and reached 87.9±2.4.

As regards to the heart rate, there was a statistically significant higher hart rate in bupivacaine and hyaluronidase group than bupivacaine only group after 2, 4, 6, 12, 18 and 24 hours of the operation but the percentage of increase (from 2 hours to 24

hours) was significantly higher in bupivacaine only group than bupivacaine and hyaluronidase group.

There was a statistically significant lower oxygen saturation in bupivacaine and hyaluronidase group than bupivacaine only group after 12 and 18 of the operation but the percentage of increase (from 2 hours to 24 hours) didn't differ significantly in both groups.

This study showed that TAP block had no effect on systolic and diastolic blood pressures, heart rate and oxygen saturation and all values were within normal during the 24 hours postoperative follow up.

The study of Marzouk *et al.,* (2020) demonstrated non-significant differences between bupivacaine and hyaluronidase group and bupivacaine only group regarding blood pressure, HR and SPO2 and all hemodynamics were normal during the 24 hours postoperative follow up (22).

Several studies about TAP block mentioned the changes in hemodynamics and all of them reported changes in the vital signs but all within normal. In the study of Baytar *et al.,* (2019) comparing the sonar-guided subcostal TAP block and quadratus lumborum block in laparoscopic cholecystectomy, the blood pressure and the heart rate were normal with no statistically significant differences between both groups (23).

Also, the study of Karasu *et al.,* (2021) about sonar-guided TAP block for postoperative analgesia in laparoscopic cholecystectomy bupivacaine only or added to ketamine and dexmedetomidine reported heart rate and mean arterial blood pressure in all groups with higher values in bupivacaine only group (24).

In the same line is the study results done by Kupiec et al. (2018) on the analgesic efficacy of transversus abdominis plane (TAP) block following caesarean section showed that systolic blood pressure, diastolic blood pressure, and heart rate were all within normal ranges in the control group and TAP block group with bupivacaine, with slightly higher values in patients who received bupivacaine (25).

Measurements of HR and MAP were normal for the first 24 hours, with maximum values at 24 hours after surgery in the study by Zahra et al., (2021) to evaluate the effect of intraperitoneal instillation of bupivacaine, bupivacaine plus dexamethasone or bupivacaine plus magnesium sulphate, on postoperative pain following laparoscopic cholecystectomy (26).

It's possible that the medicines used during surgery and to keep the patient asleep

contributed to the initial low readings. Hypovolemia from fasting before surgery and the vasodilatory and negative inotropic effects of several anesthetic induction drugs have both been linked to the decreased hemodynamic stability that might occur during this procedure (27).

During the 24 hours follow up, the study showed a statistically significant increase in the diastolic and systolic blood pressure, oxygen saturation and heart rate. This could be explained as minimal amounts of bupivacaine being absorbed and reach the circulation. Bupivacaine provides potent cardiotoxicity, it may increase heart rate and blood pressure and generate discomfort for some patients (28,29).

Regarding bupivacaine and hyaluronidase group, the patients had a statistically significant higher systolic and diastolic blood pressures, heart rate and oxygen saturation. Hyaluronidase is an enzyme that breaks down hyaluronic acid and increase the absorption of drugs into tissues with minimal systemic absorption (30).

There was statistically insignificant disparity between both groups regarding the post operative side effects. In bupivacaine and hyaluronidase group only 6 patients (20%) complained of nausea and 2 patients (6.7 %) had hypotension. On the other hand, in bupivacaine only group 8 patients (26.7 %) had nausea and 6 patients (20%) had hypotension.

Baker *et al.,* (2018) agree with the results of our study. TAP block with liposomal bupivacaine for postpartum pain management was shown to be an effective and safe treatment with little side effects, as stated in the research. Symptoms of itching, nausea and vomiting were the most often reported. (31).

Also, Marzouk et al., (2020) showed that there were statistical insignificant differences between bupivacaine and hyaluronidase group and bupivacaine only group regarding the rates of hypotension, bradycardia, pruritis, nausea, and vomiting and these complications were the most common (22).

The study of Rahimzadeh *et al.,* (2022) about TAP block in laparoscopic cholecystectomy demonstrated that no issues were caused by the block, suggesting that pain after surgery might be lessened by TAP block if the right amount of local anesthetic was applied. Dizziness, nausea, vomiting, itching, and hypotension are the most common postoperative complications associated with opiate usage (32).

In conclusion, the utilization of hyaluronidase as an adjunct to bupivacaine in

sonar-guided TAP block after laparoscopic cholecystectomy gives excellent postoperative analgesia, lowers the demand for the use of analgesics in the first few postoperative days.

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