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Intrathecal levo-bupivacaine versus hyperbaric bupivacaine for inguinal hernia repairs in ex-preterm infants: A double blinded randomized prospective study

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ABSTRACT

Background and aim: The anesthetic management of premature neonates has many challenges resulting from immature physiological adaptations, the transitional circulation, increased presence of comorbidities and, prominently, the occurrence of apnea in preterm infants. The aim of the present study was to compare the efficacy and safety of levobupivacaine with hyperbaric bupivacaine for spinal anesthesia in preterm infants scheduled for inguinal hernia repair.

Methods: A double-blinded randomized, prospective, controlled study was conducted in a tertiary care pediatric surgery center from January 2017 to February 2021 where 60 preterm infants aged <45 weeks post-menstrual age (PMA) were scheduled for an elective inguinal hernia repair procedure. Preterm infants comforted by a sugared pacifier were divided randomly into two groups (30 infants each). Group I received spinal anesthesia with 1 mg/kg 0.5% hyperbaric bupivacaine, while group II received spinal anesthesia with1mg/kg o.5% levobupivacaine. The primary objective was to assess the hemodynamic stability, sensory and motor blockade of intrathecal levo-bupivacaine compared to hyperbaric bupivacaine in premature infants, and secondarily was to monitor the incidence of postoperative apnea, length of stay (LOS), and need for postoperative ventilator support.

Results: The onset of sensory block of spinal anesthesia in group II was statistically significantly faster than in group I (Group I = 2.6 ± 0.52 min, Group II = 2.3 ± 0.35 min, $p = 0.0112$), with a statistically significant rapid regression in group II compared to group I (group I = 86 ± 2.45 min, Group II = 84 ± 3.67 min, $p = 0.016$).

Conclusions: Levo-bupivacaine is an effective and safe agent for spinal anesthesia and has an equivalent potency to hyperbaric bupivacaine for motor blockade in premature infants requiring inguinal hernia repair surgery.

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1. Introduction

Premature infants are defined as those born before 37 weeks gestation and account for about 10–13% of total births in Western literature [1]. The American Association of Pediatrics (AAP) recommended the use of the postmenstrual age (PMA), which is the sum of the gestational age (first day of the last menstrual period to the date of delivery) and chronological age (from date of birth to present) [2].

An obvious increase in the survival rate of premature births resulted in a significant number of premature infants requiring surgery. Inguinal hernias develop in 13% of premature infants [3]. The perioperative anesthetic management of neonates is a challenging experience caused by their vulnerability to respiratory and cardiac events and their immature physiological adaptation mechanisms [4]. Furthermore, problems of the transitional circulation increased incidence of comorbidities and, prominently, the occurrence of apnea in preterm [5]. Anesthetics has a neurotoxic effect on the neonatal developing brain, which is the subject of active research (GAS, PANDA) [6].

Apneas of prematurity is defined as periodic breathing with pauses that occur in preterm. Apnea is considered pathological when lasting more than 20 s, or <20 s with bradycardia, or with cyanosis, pallor, or hypotonia [7]. Cote et al. combined data from eight prospective studies (255 patients) studied risk factors for postoperative apnea and concluded that the incidence of apnea varies from 25% in the (LBW) premature to 84% in the very low birth weight (VLBW) group [8].

The administration of intravenous caffeine preoperatively can considerably decrease incidence of postoperative apnea [9], due to its neuro-stimulant effect on cardiorespiratory centers, and the neurodevelopmental consequences may be improved [10]. However, caffeine administration could cause lower weight gain and increased mortality rate. A recent study advocated its administration to only infants weighing <1250 g [11].

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In 1984, Abajian supported awake spinal anesthesia for ex-premise [12]. After that several uncontrolled studies followed signifying that spinal anesthesia has a reduced the risk for postoperative apnea compared to general anesthesia [13]. The local anesthetics delivered neuraxially in neonates tend to have cardiovascular complications (i.e., convulsions and arrhythmias) [14], due to age-related alterations in pharmacokinetics and therefore high free drug plasma concentrations following a bolus and accumulation of local anesthetic during infusion in neonates [15].

Levo-bupivacaine is the S-enantiomer of bupivacaine used as an alternative to racemic bupivacaine for regional anesthesia in adult practice, but no pharmacokinetic or pharmacodynamic data exist on its use in pediatric spinal anesthesia [16]. The aim of the present study was to compare the efficacy and safety of levo-bupivacaine to hyperbaric bupivacaine for spinal anesthesia in preterm infants scheduled for inguinal hernia repair.

2. Materials and methods

A double-blind randomized, prospective, controlled study was conducted in a tertiary care pediatric surgery center from January 2017 to February 2021 after the approval of the regional ethical committee.

A written informed consent was obtained from the parents for the participation of their children in this study. The study was approved by the ethical committee of Faculty of Medicine, Alexandria University (IRB No. 00007570, FWA No. 00018702). The sample size is approved to be sufficient by the Department of Statistics, Medical Research Institute, Alexandria University, Egypt, with 80% power of the study [7].

Sixty preterm infants aged <45 weeks postmenstrual age (PMA) of either sex was scheduled for an elective inguinal hernia repair procedure. Infants suffering from anemia, coagulopathy, history of allergic reaction to local anesthetics, uncontrolled convulsions, vertebral anomalies, multiple congenital anomalies, sepsis, or local site infection were excluded from the study.

During the preoperative visit, the assessment was completed by detailed history, clinical examination, and routine laboratory investigations. No premedication was done. All patients were fasting according to the American Society of Anesthesiology fasting rules [17]. EMLA cream was applied to the lumbar puncture site 30 minutes prior to arrival in the Operating Room (OR).

On arrival at the operation theatre with warming blankets to avoid hypothermia, a multichannel monitor was attached to the preterm infants in the form of continuous electrocardiogram, heart rate, pulse oximeter and noninvasive arterial blood pressure.

Infants were comforted by a pacifier dipped in a sugar solution, the spinal anesthesia tray as described by Abajian et al. [12] was prepared and local anesthetic preparation was randomly prepared and allocated by sealed envelope into two equal groups (30 each); Group I received spinal anesthesia with 1 mg/kg of 0.5% hyperbaric bupivacaine. Group II received spinal anesthesia with 1 mg/kg of 0.5% levobupivacaine.

The infant was positioned in a sitting posture supported by an assistant with an extended chin, under complete a septic technique, and a 25-gauge disposable Quincke spinal needle was used to perform the lumbar puncture at the most readily palpable interspace below the third lumbar vertebra through the midline approach. Once free flow of cerebrospinal fluid was obtained, the previously prepared local anesthetic was administered.

After injection, the infant was placed in the supine position, oxygen was delivered through a nasal cannula at a rate of 3 L/min. and were monitored for cessation of lower extremity movement. At that time, a lower limb intravenous cannula was inserted and secured. The dermatomal height of the spinal block was neither assessed by peripheral nerve stimulators nor by pinprick.

The immediate loss of tone in the lower limbs after spinal blockade was assumed to be above T10, while dermatomal spread above T7 was proved by the paradoxical respiratory pattern with upper limb weakness. Infants with failed spinal anesthesia were excluded from the study and anesthetized with general endotracheal anesthesia.

On completion of the operations, all infants were transferred to NICU, nasal oxygen was applied at a rate of 3 l/min, and continuous monitoring of blood pressure (BP), heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO2) were done for 12 h postoperatively. The RR and HR were measured through the attached ECG leads on the infants' chest.

The monitor alarm limit was readjusted to sound when respiration stops for more than 20 s (i.e., apnea) or if the HR falls less than 100 beats/min (i.e., bradycardia) for more than 20 s or SpO2 decreases to less than 90%.

Infants developed attacks of apnea or bradycardia in the postoperative period were managed with tactile stimulation; if there was no response, bag and O2 mask ventilation together with airway positioning and suctioning were done. Resistant bradycardia despite previous measures treated with intravenous atropine 0.01 mg/kg. Infants who developed apnea attack were kept on O2 therapy in NICU for a further 12 h. Noninvasive BP was observed, and evidence of hypotension (i.e., MABP falls below the fifth or tenth percentile for gestational and postnatal age) [18], was treated with 10 ml/kg intravenous normal saline.

Table 1. Modified bromage score [19].

Grade	Criteria	Degree of block
I	Free movement of legs& feet	None
II	Just able to flex knees with free movement of feet	Partial 33%
III	Unable to flex knees with free movement of feet	Partial 66%
IV	Unable to move legs and feet	Complete paralysis

Demographic information (chronological age, gestational age, sex, weight), history of apnea, hemodynamic measurements including heart rate, mean arterial blood pressure (MABP), and oxygen saturation (before and immediately after spinal anesthesia, after onset of motor blockade, at the starting of surgical incision, then every 5 min for 20 min throughout surgical procedure, at the end of operation, and hourly for 12 hours postoperative), number and timing of apnea, bradycardia, and hypotensive attacks, onset of motor blockade, duration of motor blockade assessed by Bromage score (Table 1) [19], level of dermatomal sensory blockade, duration of sensory blockade assessed by premature infant pain profile (PIPP) score (Table 2) [20], postoperative need for ventilator support, and length of stay (LOS).

2.1. Outcomes of the study

The primary outcomes included assess the hemodynamic stability, sensory and motor blockade of intrathecal levo-bupivacaine compared to hyperbaric bupivacaine in premature infants, and secondary outcomes was to monitor the incidence of postoperative apnea, length of stay (LOS), and need for postoperative ventilator support.

2.1.1. Statistical analysis method

Data were evaluated using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov test was used to validate the normality of variables distribution, categorical variables comparison was evaluated using Chi-square test (Fisher or Monte Carlo). Student t-test was implied to compare the two groups for normally distributed quantitative variables. Kaplan – Meier survival curves, to estimated survival times for the spinal anesthesia among the studied groups. The significance of the obtained results was refereed at the 5% level.

3. Results

A flowchart of the study population is shown in Figure 1. Of the 72 in ex-preterm infants undergoing inguinal herniorrhaphy was conducted in a tertiary care pediatric surgery center from January 2017 to February 2021. Twelve patients were excluded from the study (2 patients declined consent and 10 patients did not meet the inclusion criteria, 60 patients were willing to participate in the study and were divided into two groups, spinal anesthesia with 1 mg/kg of 0.5% hyperbaric bupivacaine ($n = 30$) and levo bupivacaine ($n = 30$).

Demographic data including (Gestational age, chronological age, PMA, sex, weight), and duration of surgery showed no statistically significant difference between the two studied groups ($p > 0.05$), most of the preterm infants included in the present study had a history of apnea with statistical insignificant difference between the two groups ($p = 0.085$), (Table 3).

There were no significant differences in heart rate, respiratory rate, or oxygen saturation between the two studied groups ($p > 0.05$), while MABP was significantly lower with hyperbaric bupivacaine immediately after spinal anesthesia (Group I = 40.4 ± 3.7, Group II = 42.3 ± 1.6, $p = 0.012$) and after onset of motor blockade (Group I = 39.8 ± 2.7, Group II = 41.4 ± 1.3, $p = 0.004$) responded to bolus of 10 ml/kg intravenous normal saline (Table 4).

Regarding complete motor blockade (modified Bromage score ≥ 3) the onset was statistically significant earlier in group I compared to group II (Group I = 2.8 ± 0.53 min, Group II = 3.2 ± 0.76 min, $p = 0.0214$) with a statistically significant longer duration in group I compared to group II (Group I = 81 ± 5.34 min, group II = 78 ± 3.48 min, $p = 0.0125$). Whereas the sensory blockade (PIPP ≤ 2) was statistically significant faster in group II compared to group I (Group I = 2.6 ± 0.52 min,

Table 2. Premature infant pain profile [20].

	Score			
Indicators	0	1	2	3
Gestational age	36 weeks or more	32–35 weeks +6 days	28–31 weeks +6 days	Less than 28 weeks
Behavioral state	Active, awake, eyes open, facial movements	Quiet, awake, eyes open, no facial movements	Active, awake, eyes closed, facial movement	Quiet, asleep, eyes closed, no facial movements
Heart rate maximum	0 bpm increase	5–15 bpm increase	15–24 bpm increase	24 bpm increase
O2sats	92–100%	89–91%	85–88%	84% or less
Brow bulge	None	Minimum	Moderate	Minimum
Eye squeeze	None	Minimum	Moderate	Minimum
Naso-labial furrow	None	Minimum	Moderate	Minimum

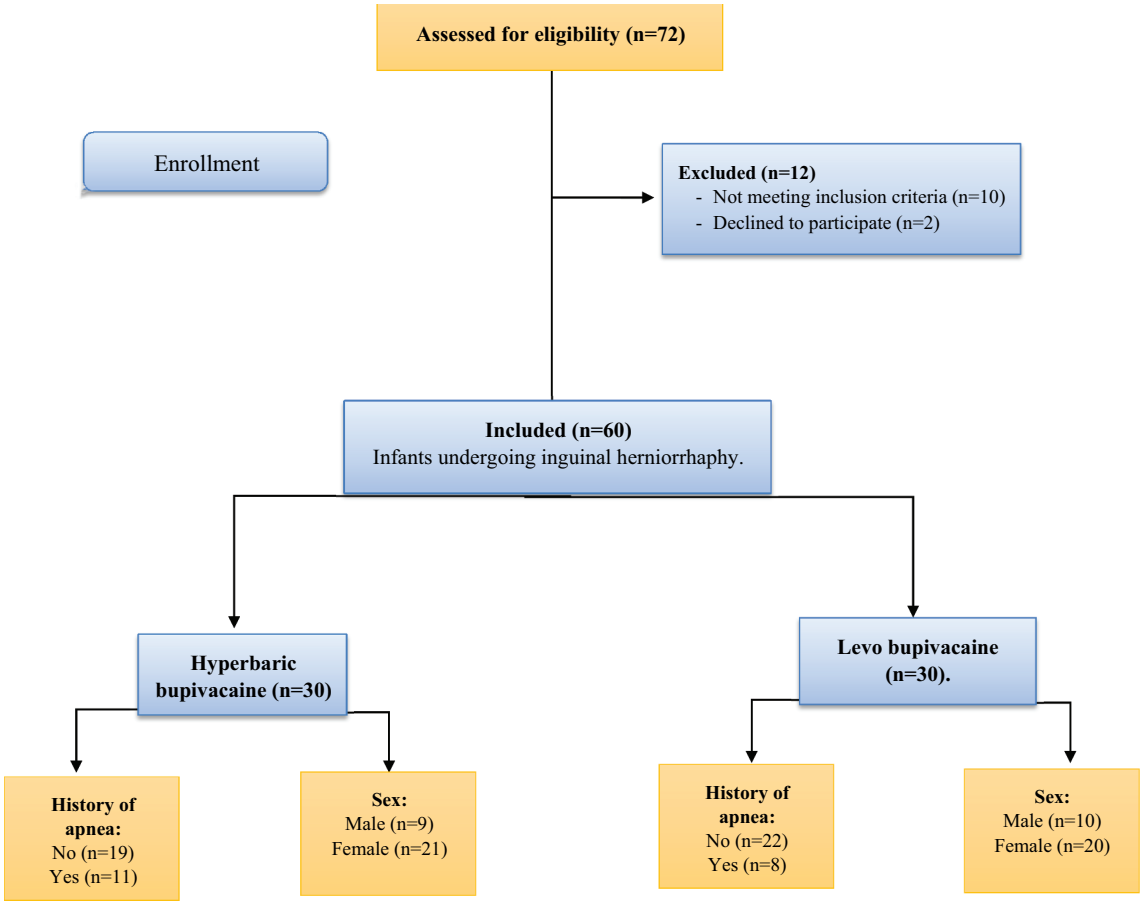

Figure 1. Flowchart of infants undergoing inguinal herniorrhaphy.

Table 3. Demographic data among spinal anesthesia with 1 mg/kg of 0.5% hyperbaric bupivacaine and levo bupivacaine studied groups.

	Spinal anesthesia with 1 mg/kg of 0.5%			
Variables	Hyperbaric bupivacaine ($n = 30$)	Levo bupivacaine ($n = 30$)	*U*	*p value*
Chronological age/years				
Mean ±SD	1.50 ± 0.90	1.30 ± 1.10	24.76	0.167
Range	1.00–2.50	1.00–2.50		
Gestational age/weeks				
Mean ±SD	36.03 ± 1.29	37.53 ± 1.02	11.98	0.588
Range	22.00–38.00	25.00–39.00		
PMA/weeks				
Mean ±SD	32.41 ± 8.23	35.62 ± 4.23	37.09	0.120
Range	20.00–45.00	22.00–45.00		
Sex (N, %)				
Male	9 (30.00%)	10 (33.33%)	$X^2=1.05$	0.841
Female	21 (70.00%)	20 (66.67%)		
Weight/kg				
Mean ±SD	4.22 ± 0.61	3.89 ± 0.93	12.99	0.453
Range	3.00–5.00	3.00–5.00		
Duration of surgery/min				
Mean ±SD	37.68 ± 8.41	39.45 ± 6.52	41.02	0.073
Range	30.00–50.00	30.00–50.00		
History of apnea				
No	19 (63.33%)	22 (73.33%)	$X^2=2.61$	0.085
Yes	11 (36.67%)	8 (26.67%)		

Post-menstrual age (PIMA), Mann Whitney u test (U), Chi square test (X^2).

Group II = 2.3 ± 0.35 min, $p = 0.0112$), with a statistically significant rapid regression in group II compared to group I (group I = 86 ± 2.45 min, Group II = 84 ± 3.67 min, $p = 0.016$). Only one case in each group experienced one attack of postoperative apnea associated with bradycardia on 3.5 h and 4 h in groups I and II, respectively, with no significant difference between the two studied groups ($p = 1.00$), responding to tactile stimulation, furthermore the length of hospital stay was statistically insignificant between both groups (Group 1 = 25 ± 2.2 h, Group II = 26 ± 2.1 h, $p = 0.076$) (Table 5).

Table 4. Vital science among spinal anesthesia with 1 mg/kg of 0.5% hyperbaric bupivacaine and levo bupivacaine studied groups.

Variables	Spinal anesthesia with 1 mg/kg of 0.5% Hyperbaric bupivacaine ($n = 30$)	Levo bupivacaine ($n = 30$)	*U*	*p value*
Heart rate				
Mean ±SD	145.70 ± 5.50	142.33 ± 8.27	13.29	0.412
Range	134.00–154.00	132.00–154.00		
Respiratory rate				
Mean ±SD	44.13 ± 5.22	41.73 ± 2.63	9.52	0.812
Range	36.00–46.00	38.00–46.00		
Oxygen saturation				
Mean ±SD	97.52 ± 1.04	96.43 ± 1.67	10.40	0.730
Range	95.00–99.00	94.00–99.00		
MABP after Spinal anesthesia				
Mean ±SD	40.4 ± 3.7	42.3 ± 1.6	56.99	0.012*
Range	36.70–44.10	40.70–43.90		
After onset of motor blockade				
Mean ±SD	39.8 ± 2.7	41.4 ± 1.3	46.21	0.004*
Range	37.10–42.50	40.10–42.70		

Initial mean arterial blood pressure (MABP), Mann Whitney u test (U), Chi square test (X^2), *: Significant.

Table 5. Outcome among spinal anesthesia with 1 mg/kg of 0.5% hyperbaric bupivacaine and levo bupivacaine studied groups.

Variables	Spinal anesthesia with 1 mg/kg of 0.5% Hyperbaric bupivacaine ($n = 30$)		Levo bupivacaine ($n = 30$)		U	*p value*
The onset/min						
Mean ±SD	2.8 ± 0.53		3.2 ± 0.76		29.07	0.0214*
Range	2.00–4.00		2.00–4.00			
Duration/min						
Mean ±SD	81 ± 5.34		78 ± 3.48		30.84	0.0125*
Range	75.00–86.00		74.00–82.00			
PIPP ≤2						
Mean ±SD	2.6 ± 0.52		2.3 ± 0.35		69.21	0.0112*
Range	2.00–4.00		2.00–3.00			
Rapid regression						
Mean ±SD	86.00 ± 2.45		84.00 ± 3.67		321.60	0.016*
Range	83.00–89.00		80.00–88.00			
One attack of postoperative apnea associated with bradycardia on 3.5 and 4 h	No.	%	No.	%	X^2=0.00	1.00
	1	3.33	1	3.33		
Length of hospital stay/h						
Mean ±SD	25 ± 2.2		26 ± 2.10		5.33	0.076
Range	22.00–28.00		23.00–29.00			

Premature infant pain profile (PIPP), Mann Whitney u test (U), Chi square test (X^2), *: Significant.

According to Kaplan – Meier survival curves, estimated median survival times was significantly higher among hyperbaric bupivacaine group (81.00, 95% CI: 79.390–82.610) than levo bupivacaine groups (78.00, 95% CI: 77.105–78.895) minutes (log-rank test, $p < 0.001$). As well a, the amount of spinal anesthesia with 1 mg/kg of 0.5% hyperbaric bupivacaine and levo bupivacaine have a statistically significant link (Table 6, Figure 2).

4. Discussion

Anesthesia for premature infants has many challenges resulting from immature physiology and incomplete organogenesis [21]. Premature infants are prone to apneas [22]. The spinal anesthesia (SA) used in premature infants increased considerably as its reinvention by Abajian et al. [12] Levo-bupivacaine has been endorsed as an alternative to bupivacaine with lesser

Table 6. Means and medians for survival time using Kaplan – Meier survival analysis among hyperbaric bupivacaine and levo bupivacaine groups.

Spinal anesthesia with 1 mg/kg of 0.5%	Mean				Median			
			95%CI				95% CI	
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Hyperbaric bupivacaine	81.200	0.562	80.098	82.302	81.000	0.822	79.390	82.610
Levo bupivacaine	78.367	0.400	77.583	79.150	78.000	0.456	77.105	78.895
Overall	79.783	0.388	79.022	80.545	79.000	0.704	77.620	80.380
Log Rank (Mantel-Cox)								
Chi-Square (X^2)				18.611				
Sig. (*p value*)				<0.001*				

Confidence Interval (CI), *Significant.

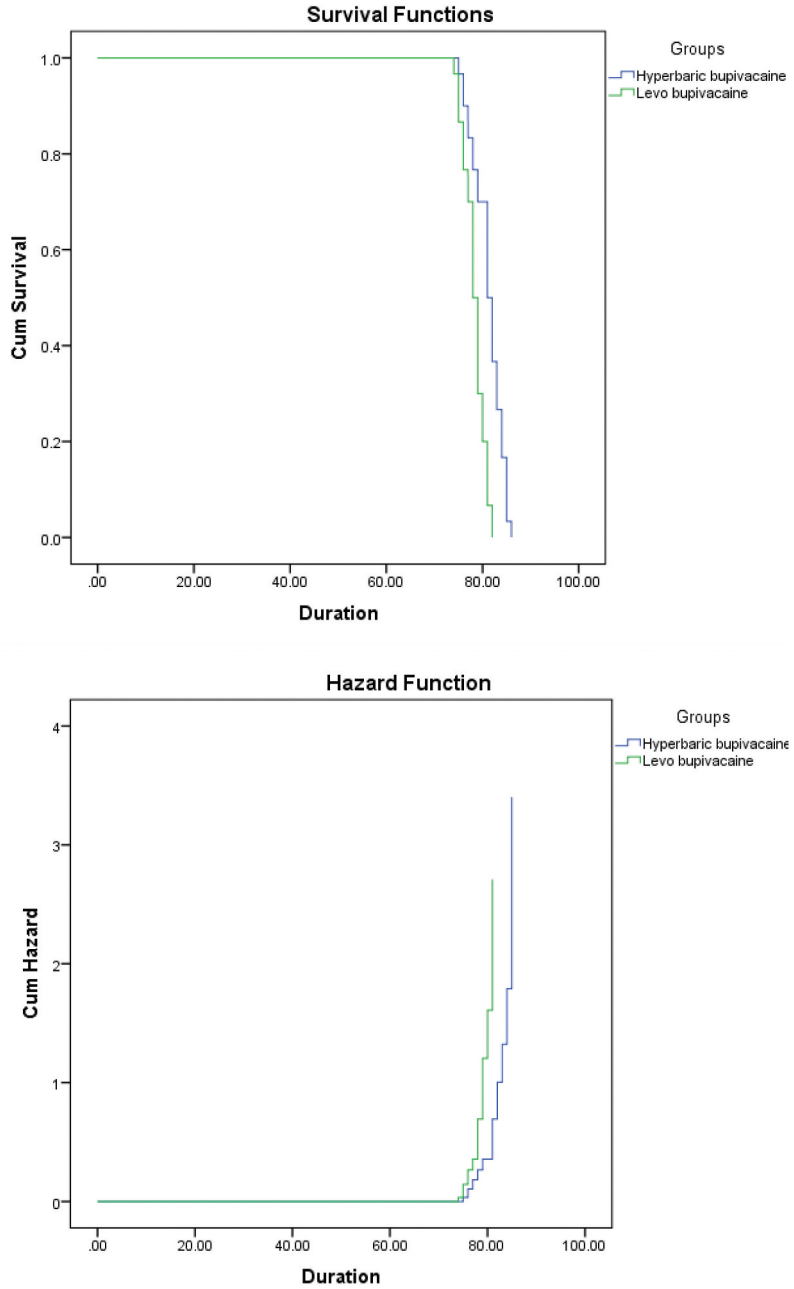

Figure 2. Survival and hazard function for survival time using Kaplan – Meier survival analysis among hyperbaric bupivacaine and levo bupivacaine groups.

cardiotoxicity [23]. The present study aimed to compare the efficacy and safety of levo-bupivacaine to hyperbaric bupivacaine for spinal anesthesia in preterm infants.

The present study showed that group I infants suffered from hypotension compared to group II, especially immediately after spinal anesthesia and after the onset of motor blockade. In contrast to the present results, Dohi *et al*. revealed that SA produces no hypotension in infants explained by under development of the sympathetic nervous system [24]. In addition, Oberlander et al. concluded that hemodynamic stability was the consequence of a decrease in parasympathetic cardiac modulation [25]. Whereas in agreement with the present results, Bonnet et al. [26] stated a significant decrease in MABP at 5 and 10 min after SA in premature infants due to larger doses of bupivacaine required in infants due to the larger volume of distribution and to the relative increased surface area of the spinal cord and nerve roots [27].

Concerning complete motor blockade, the onset and duration was statistically significant earlier and longer, respectively, in group I compared to group II. Likeminded with the present study, Frawley et al. [28] documented that motor blockade of levo-bupivacaine was relatively short duration compared to bupivacaine used intrathecally in neonates.

Regarding sensory blockade, the onset and regression were statistically significantly faster in group II in comparison with group I. In agreement with the results

of present study Kokki et al. [29] studied SA in pediatrics scheduled for infra-umbilicus surgery and established that regression of sensory blockade was faster in the levo-bupivacaine group than the bupivacaine group.

As regards postoperative apnea attacks associated with bradycardia occurred, only one case in each group with 3.5 h and 4 h in groups I and II, respectively, responding to tactile stimulation, these two cases were twined (42 weeks PMA) and had gestational age 30 weeks. Agreeing with the present study, Davidson et al. [30] studied the rates of postoperative apnea between general anesthesia (GA) versus spinal anesthesia (SA) on 722 young infants younger than 60 weeks PMA, scheduled for inguinal herniorrhaphy, and concluded that the incidence of postoperative apnea was 6.1% in prematurely born and 0.3% in full-term infants and was not altered with SA or GA. However, the incidence of early apnea was less in awake SA, while late onset of apnea occurred in two infants on 6 to 7 h postoperatively in SA group. In our study, Kaplan – Meier survival curves, estimated median survival times were significantly higher among hyperbaric bupivacaine group than levo bupivacaine groups.

4.1. Limitation of the study

Small sample size of the studied patients, so we hope mere studies including large number of patients in different study areas.

5. Conclusion

Levo-bupivacaine is an effective and safe agent for spinal anesthesia and has an equivalent potency to hyperbaric bupivacaine for motor blockade in premature infants requiring inguinal hernia repair surgery.

Abbreviations

LBW	low birth weight;
VLBW	very low birth weight;
EMLA	Eutectic mixture of local anesthetics;
NICU	Neonatal intensive care unit;
PMA	Post menstrual age.

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Availability of data and material

All data supporting the study are presented in the manuscript or available upon request.

Authors' contributions

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Consent for publication

All authors have read and revised well for the manuscript and agree to publishing.

Ethics approval and consent to participate

A written informed consent was obtained from the parents for the participation of their children in this study. The study was approved by the ethical committee of Faculty of Medicine, Alexandria University (IRB No. 00007570, FWA No. 00018702).

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