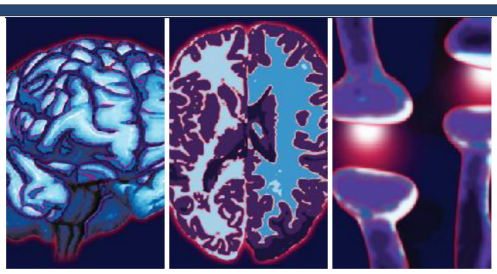
Research Article



Impact of Combined Spinal Epidural Analgesia on Biomolecular Mediators in Painless Labor: Insights from an Experimental Study in Indonesia.

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ABSTRACT

Background: Inflammation affects labor by influencing contractions and dilation. Pain, often linked to tissue ischemia, involves mediators like Tumour Necrosis Factor (TNF-α), Substance P (SP), and Nitric Oxide (NO). Neuraxial analgesia, including combined Spinal Epidural Analgesia (SEA) with levobupivacaine, is preferred for its effectiveness and minimal side effects in painless labor. This study investigates these effects in parturient undergoing SEA with levobupivacaine, contributing to the development of novel pain medications and enhancing obstetric care.

Methods: This study was conducted at Permata Hati Metro Hospital in Indonesia. 60 expectant mothers in active labor or in the third trimester scheduled for vaginal delivery were enrolled. Blood serum samples were collected for analysis, and to be processed by Enzyme Immuno Sorbent Assay (ELISA) Kit for determining serum levels of TNF-α, SP, and NO.

Results: Following treatment, there were no significant differences in TNF-α levels between groups before and after treatment ($p>0.05$). Although no significant difference in SP levels was noted before treatment, a significant difference was evident after treatment ($p<0.05$). Moreover, a significant reduction in NO levels was observed in the SEA group compared to the control group ($p<0.05$). SEA significantly relieved labor pain compared to the control group ($P<0.05$), accompanied by notable improvements in vital signs and Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores and labor duration ($P<0.001$).

Conclusion: SEA with levobupivacaine during painless labor demonstrates a trend of decreasing TNF-α and SP levels while significantly reducing NO levels. Although some mediators did not show significance, clinical benefits were found in patients and babies.

Keywords: Neuraxial analgesia, labor pain, tumor necrosis factor-alpha, substance P, nitric oxide

Introduction

Pain emerges as a result of the inflammatory process in labor. It is often associated with the process of tissue ischemia that may lead the release of various pro-inflammatory and anti-inflammatory mediators, including

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TNF-α, Substance P (SP), and Nitric Oxide (NO). TNF-α, in response to tissue ischemia, increases afferent fiber activity and promotes contractions during labor [1]. Pro-inflammatory cytokines also enhance substance P release, facilitating pain transmission *via* NK1 protein binding in the spinal cord [2]. Physiologically, NO is synthesized by vascular endothelium, acting as a potent endogenous vasodilator while inhibiting neutrophil accumulation and platelet aggregation [3]. Advancements in understanding the neurophysiology and neuropharmacology of pain, along with insights into nociceptive pain transmission in the spinal medulla, contribute to the development of optimal pain management strategies during labor [4]. Utilizing anesthesia agents capable of modulating neural transmission enables effective analgesia with minimal autonomic and motor nerve blockade.

Neuraxial analgesia, particularly combined Spinal Epidural Analgesia (SEA), is preferred during labor due to its ability to provide effective pain relief without hindering the natural progression of labor or leading to notable side effects. Levobupivacaine, an analog of bupivacaine, is frequently utilized owing to its similar effectiveness and reduced risk of toxicity to both the central nervous and cardiovascular systems compared to other agents [5]. Although there is no one-size-fits-all approach, neuraxial techniques are generally regarded as the optimal choice for the majority of mothers [6]. Through this study, we delve into the repercussions of administering combined SEA with levobupivacaine on painless labor within Indonesia to find the biomolecular mechanisms intertwined with natural childbirth. Such insights could potentially pave the way for the refinement of forthcoming pain management approaches. Our research endeavors to illuminate the levels of Tumor Necrosis Factor-alpha (TNF-α), Substance P (SP), and Nitric Oxide (NO) in parturients, postulating a reduction in these markers subsequent to the administration of SEA with levobupivacaine.

Materials and Methods

Study design and protocol

The experimental study adopts a concealed Randomized Control Trial (RCT) design, comprising treatment and control groups. The treatment group, consisting of first-stage parturients, receives combined SEA using levobupivacaine, while the control group does not (Figure 1). The sample comprises pregnant females in labor or third-trimester women expected to be in labor, meeting inclusion criteria, and providing informed consent at Permata Hati General Hospital, Lampung, Indonesia. Inclusion criteria involve consecutive sampling of primigravida to multigravida patients, up to four, without a history of cesarean section. The exclusion criteria of this study is parturients expected to be unsuitable for normal delivery, those with a history of or undergoing cytostatic drug treatment, pre-existing metabolic disorders like hypertension and diabetes, and contraindications to SEA. Eligible patients are proceed to sign informed consent forms, and then to be divided into treatment and control groups.

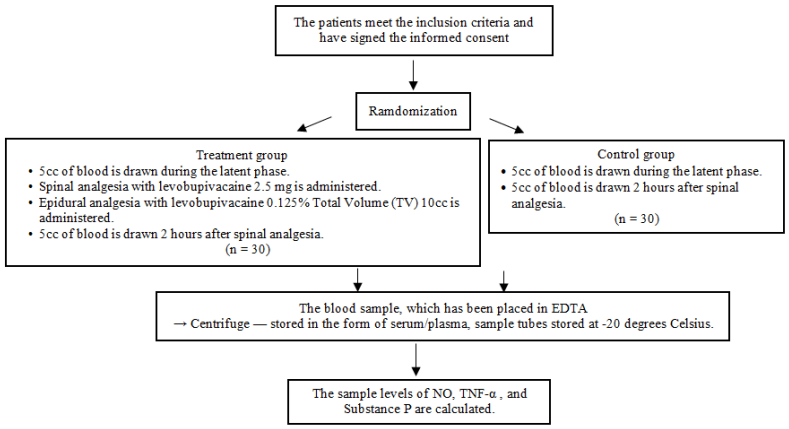

Figure 1. Study protocol first-stage parturients, receives combined SEA using levobupivacaine.

▪ Data measurements

Sample preparation is carried out in the Clinical Pathology Laboratory of Permata Hati General Hospital. The measurement of TNF-α, SP, and NO levels will be conducted for the samples, which is the patients blood serum. The dependent variables of this study are TNF-α levels, SP levels, NO levels, Visual Analog Scale (VAS) score, and APGAR score. The independent variable of this study is SEA with levobupivacaine. In addition, the examination of VAS scores will be conducted using a numerical rating scale table.

▪ Levobupivacaine injection

The vials contain 10 cc of levobupivacaine 0.5% isobaric. Levobupivacaine is being administered at 2.5 mg for spinal anesthesia and a total volume of 10 cc of 0.125% for epidural anesthesia, with an additional 5 cc per hour. In the treatment group, 0.5 cc of levobupivacaine 0.5% is intrathecally injected, followed by a slow epidural injection of 10 cc of 0.125% levobupivacaine one hour later, while closely monitoring vital signs and adverse reactions.

▪ Sample collection

Blood samples are collected from a vein, totaling 3 ml each to determine TNF-α, SP, and NO levels. The baseline data is obtained by the first sample that is taken 5 minutes before the SEA procedure (considered as minute 0). The next samples are taken after 90 minutes of the SEA procedure. Enzyme Linked Immuno Sorbent Assay (ELISA) kit is used for the determination of serum TNF-α, SP, and NO levels.

▪ Ethical consideration

This research has received an ethical approval from the Medical and Health Research Ethics Committee Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada Yogyakarta, Indonesia, with the referral number of KE/FK/0261/EC/2022. Informed consent was obtained from all the subjects involved.

▪ Statistical methods

Data analysis using the Statistical Package for Social Sciences version 23. The steps are univariate analysis, used for describing the characteristics of each variable studied using the frequency distribution and percentage of each group, then the data is displayed in table and narrative form. Bivariate analysis, used for identifying is there any relationship between the independent variable and the dependent variable, and the dependent variable and external variables. Multivariate analysis, used for determining the independent relationship between the dependent variable controlled and external variables, calculated using several models Analysis of Variance (ANOVA and logistic regression). This analysis is aimed to comprehend the relationship between levobupivacaine SEA and the levels of TNF-α, substance P, NO, VAS, APGAR and labor duration.

Results

The study comprises 60 expectant mothers in labor or the third trimester at Permata Hati Metro Hospital, selected through consecutive sampling by the researcher. Inclusion criteria involve primigravida to multigravida up to the fourth without a history of cesarean section. Six participants dropped out, four in the SEA group due to unsuccessful progression in labor leading to cesarean section, and two in the control group undergoing cesarean delivery, totaling six dropouts in both groups. The data will be presented based on time, which involves the result before treatment (T0) and after treatment (T1), and also based on process, which involves the result before treatment (T0) and post-partum levels (T2).

▪ Cytokines levels in the SEA group and control group based on time and process

In this study, differences in TNF-α, SP and NO levels were observed between the SEA and Control groups, as shown in the Table 1.

Table 1: Cytokines levels in the SEA and control groups based on time.

		NO		
Group	**T0**	**T1**	**T1-T0**	**P-Value**
SEA	17379.5 (1833-124019)	8441 (2334-94432)	-4753.5 (-120703, -23016)	0.028[a]
Control	39332.5 (7949-76048)	36035.5 (2135-91407)	-4741.5 (-22742, -52568)	0.098 [a]
p	0.000 [b]	0.000 [b]	0.442 [b]	-

		TNF-α		
Group	**T0**	**T1**	**T1-T0**	**P-Value**
SEA	10118 (0.022-52023)	9124 (3500-26169)	3477 (-21266, -35117)	0.111[a]
Control	10252.5 (4822-21949)	8832.5 (4856-53132)	1701 (-46682, -10503)	0.147[a]
p	0.690[b]	0.918[b]	0.098[b]	-
		Substance P		
Group	**T0**	**T1**	**T1-T0**	**P-Value**
SEA	272.83 (182-383)	288 (339-499)	223 (-209, -199)	0.318
Control	267 (258-314)	247 (264-306)	-744 (-768, -578)	0.066
p	0.46	0.005*	0.086	-

▪ Wilcoxon test mann whitney test

Assessment of TNF-α levels before treatment (T0) showed no significant difference between the SEA and control groups, with median levels of 10118 and 10252.5, respectively, and a p-value of 0.690 ($p>0.05$). Similarly, after treatment (T1), no significant difference was observed, with median levels of 9124 in the SEA group and 8832.5 in the control group, and a p-value of 0.918 ($p>0.05$). The median decrease in TNF-α levels post-treatment indicated no statistically significant difference between the two groups, with values of 3477 for the SEA group and 1701 for the control group, along with a p-value of 0.098 ($p>0.05$).

Pairwise comparisons within both the SEA and control groups yielded p-values of 0.111 and 0.147, respectively ($p>0.05$), indicating no significant difference in the change in TNF-α levels before and after treatment in either group. Assessment of Substance P (SP) levels at baseline (T0) showed a median of 272.83 in the SEA group and 267 in the control group, with a p-value of 0.460 ($p>0.05$), indicating no significant difference. Post-treatment (T1), the SEA group had a median of 288 and the control group had a median of 247, with a p-value of 0.005 ($p<0.05$), signifying a significant difference. The median decrease in SP levels was 223 in the SEA group and -744 in the control group, with a p-value of 0.086 ($p>0.05$), indicating no statistically significant difference.

Pairwise comparison within the SEA group yielded a p-value of 0.318 ($p>0.05$), indicating no significant difference in the change in Substance P (SP) levels before and after treatment. Similarly, pairwise comparison within the control group yielded a p-value of 0.066 ($p>0.05$), indicating no significant difference in the change in SP levels before and after treatment in the control group. Assessment of NO levels based on time revealed a significant difference between the SEA and control groups before treatment (T0), with median levels of 17379.5 and 39332.5, respectively, and a p-value of 0.000 ($p<0.05$).

Similarly, after treatment (T1), a significant difference persisted, with median levels of 8441 in the SEA group and 36035.5 in the control group, along with a p-value of 0.000 ($p<0.05$). However, the median decrease in NO levels post-treatment showed no statistically significant difference between the two groups, with values of -4753.5 for the SEA group and -4741.5 for the control group, and a p-value of 0.442 ($p>0.05$). Pairwise comparison within the SEA group yielded a statistically significant p-value of 0.028 ($p<0.05$), indicating a notable difference in NO levels before and after treatment. Conversely, within the control group, pairwise comparison resulted in a p-value of 0.098 ($p>0.05$), signifying no significant alteration in NO levels before and after treatment (Table 2).

▪ Wilcoxon test mann whitney test

Assessment of TNF-α levels based on process in the SEA group before treatment revealed a median level of 10118, while in the control group, it was 10252.5, with a p-value of 0.690 ($p>0.05$), indicating no significant difference between the two groups before treatment (T0). Furthermore, no significant difference was found in TNF-α levels post-delivery (T2) in the SEA group with a median of -273 and the control group with a median of 11564, with a p-value of 0.478 ($p>0.05$). The median delta TNF-α level was found to be -273 in the SEA group and 11564 in the control group, with a p-value of 0.988 ($p>0.05$), indicating no statistically significant difference between the two groups. Pairwise comparisons within

both the SEA and control groups revealed non-significant differences in TNF-α level changes, with p-values of 0.478 and 0.116 (p>0.05), respectively. This suggests that TNF-α levels remained stable within both groups following treatment.

Assessment of Substance P (SP) levels based on the process in the SEA group before treatment yielded a median level of 272.83, while in the control group it was 267 with a p-value of 0.460 (p>0.05), indicating no significant difference between the two groups before treatment (T0). Furthermore, no significant difference was found in SP levels post-delivery (T2) in the SEA group with a median of 245 and the control group with a median of 262 with a p-value of 0.193 (p>0.05). The median delta SP levels were found to be -310 in the SEA group and -191 in the control group, with a p-value of 0.225 (p>0.05), indicating no statistically significant difference between the two groups. Pairwise comparison within both the SEA and control groups showed no significant difference in the change in Substance P (SP) levels, with p-values of 0.082 and 0.213 (p>0.05), respectively, indicating that SP levels remained stable in both groups.

Assessment of NO levels in the SEA group before treatment yielded a median level of 17379.5, and in the control group, it was 39332.5, with a p-value of 0.000 (p<0.05), indicating a significant difference between the two groups before treatment (T0). Furthermore, significant differences were found in NO levels postpartum (T2) in the SEA group with a median of 8740 and the control group with a median of 35774, with a p-value of 0.000 (p<0.05). The median decrease in NO levels was -980.10 ± 2780.21 in the SEA group and -4031.5 in the control group, with a p-value of 0.859 (p>0.05), indicating no statistically significant difference between the two groups. Pairwise comparisons within both the SEA and control groups showed no significant difference in the change in NO levels, with p-values of 0.054 and 0.171 (p>0.05), respectively. This indicates that NO levels remained consistent before and after treatment in both groups.

▪ The VAS values of the SEA and control groups

In this study, differences in VAS values were observed between the SEA and Control groups, as shown in the Table 3. Based on the results of the above research, it is known that before treatment (T0), the VAS scores in the SEA group were an average of 5.3 ± 0.65, and in the control group, the VAS scores were an average of 5.4 ± 0.67. The Mann-whitney statistical test yielded a p-value of 0.508 (p>0.05), indicating that there was no statistically significant difference in the pain level between the SEA and control groups. At measurement T1 based on time, the VAS score for the SEA group was 1.67 ± 0.66, and for the control group, it was 7.50 ± 0.51, with a p-value of 0.000 (p<0.05). Based on these results, there was a statistically significant difference between the SEA and control groups. There was a statistically significant difference in the assessment of VAS scores based 0.65) with a p-value of 0.000 (p<0.05).

Table 2: Cytokines levels in the SEA and control groups based on process.

			TNF-α	
Group	**T0**	**T2**	**T2-T0**	**P Value**
SEA	10118 (0.022-52023)	10182 (5366-35564)	-273 (-23637, -25046)	0.478[a]
Control	10252.5 (4822-21949)	11564 (4637-28393)	-1045 (-17062, -284)	0.116[a]
p	0.690[b]	0.473[b]	0.988[b]	-
			Substance P	
Group	**T0**	**T2**	**T2-T0**	**P Value**
SEA	272.83 (182-383)	245 (902-469)	-310 (-267, -157)	0.082
Control	267 (258-314)	262 (206-316)	-191 (-544, -877)	0.213
p	0.46	0.193	0.225	-

			NO	
Group	**T0**	**T2**	**T2-T0**	**P Value**
SEA	17379.5 (1833-124019)	8740 (1138-104094)	-4908 (-114184, -5087)	0.054[a]
Control	39332.5 (7949-76048)	35774 (12196-149096)	-4031.5 (-51436, -94171)	0.171[a]
p	0.000[b]	0.000[b]	0.859[b]	-

Table 3: VAS scores for SEA group and control group.

	VAS		
Group	**T 0**	**T1**	**T2**
SEA	5.3 ± 0.65	1.67 ± 0.66	1.97 ± 0.61
Control	5.4 ± 0.67	7.50 ± 0.51	2.33 ± 0.65
P	0.508	0.000*	0.000*

▪ Vital signs of SEA and control groups

In this study, differences in vital signs were observed between the SEA and control groups, as shown in the Table 4. The assessment results of vital signs, including blood pressure, pulse rate, and respiratory rate, in both the SEA and Control groups after the intervention showed significant differences. The mean systolic blood pressure in the SEA group was 93.83 ± 4.57 mmHg compared to 126.33 ± 8.89 mmHg in the control group, with a P-value<0.005. Diastolic blood pressure in the SEA group had a mean of 80.77 ± 5.74 compared to 96.17 ± 26.75 in the control group, with a P-value<0.005. Pulse rate measurements also showed significant differences between the two groups, with the SEA group having a mean pulse rate of 85.77 ± 3.47 beats per minute compared to 107.63 ± 6.35 beats per minute in the control group, with a P-value<0.005.

Similarly, respiratory rate measurements revealed significant differences in mean values between the two groups, with the SEA group having a mean respiratory rate of 18.10 ± 1.40 breaths per minute compared to 24.33 ± 2.40 breaths per minute in the control group, with a P-value<0.005. Temperature measurements in both groups did not show significant differences, with the SEA group having a mean temperature of 37.17 ± 0.20 degrees Celsius and the control group having a mean temperature of 37.18 ± 0.16 degrees Celsius, with a P-value of 0.814.

▪ The APGAR score value of group SEA and control

In this study, differences in VAS values were observed between the SEA and control groups, as shown in the Table 5. The APGAR scores at 1 minute were 7.33 ± 0.61 in the SEA group and 7.00 ± 0.53 in the control group, with a significant difference (p=0.024, P<0.05). At 5 minutes, scores were 8.43 ± 0.57 and 8.10 ± 0.61, respectively, also significantly different (p=0.035, P<0.05). Similarly, at 10 minutes, scores were 9.60 ± 0.63 and 9.33 ± 0.55, respectively, with a significant difference (p=0.043, P<0.05). Overall, the SEA group displayed significant differences in mean APGAR scores at 1, 5, and 10 minutes.

▪ The duration of labor in the SEA and control groups

In this study, the difference in the duration of labor was observed between the SEA and Control groups as shown in the Table 6. Based on the above research results, it is known that the duration of labor in the SEA group is an average of 357.37 ± 19.34 minutes, while in the control group, the duration of labor is an average of 702.57 ± 893.73 minutes. The Mann-Whitney statistical test yielded a p-value of <0.001 (p<0.05), indicating a significant difference in the duration of labor between the SEA group and the control group. Therefore, it can be concluded that the additional SEA therapy effectively accelerates the duration of labor in laboring patients.

Table 4: Vital signs for SEA group and control group.					
	Vital Signs				
Group	**Systole**	**Diastole**	**Pulse**	**Temperature**	**Respiratory rate**
SEA	103.83 ± 4.57	80.77 ± 5.74	85.77 ± 3.47	37.17 ± 0.20	18.10 ± 1.40
Control	126.33 ± 8.89	96.17 ± 26.75	107.63 ± 6.35	37.18 ± 0.16	24.33 ± 2.40
P Value	0.000*	0.000*	0.000*	0.814	0.000*

Table 5: APGAR score values of SEA group and control group.			
		APGAR Score	
	ASE	**Control**	**P Value**
APGAR 1	7.33 ± 0.61	7.00 ± 0.53	0.024*
APGAR 5	8.43 ± 0.57	8.10 ± 0.61	0.035*
APGAR 10	9.60 ± 0.63	9.33 ± 0.55	0.043*

Table 6: Duration of labor in the SEA and control groups.			
		Group	
	SEA	Control	P Value
Labor duration	357.37 ± 19.34	702.57 ± 893.73	0.000*

Discussion

In this study, TNF-α levels were assessed in both the SEA and control groups, focusing on timing and process, and showed no significant differences before and after treatment (P>0.05). Pairwise comparisons within both groups further revealed no significant changes (P>0.05), which align with findings from some studies but contrast with others. TNF-α plays a vital role in childbirth physiology by triggering uterine contractions and cervical ripening. Although TNF-α mRNA levels typically increase during painful delivery, this study found no significant differences (P>0.05). Epidural analgesia may insignificantly reduce TNF-α levels during painless childbirth, necessitating further investigation.

Substance P (SP) levels were also examined for comparison in this study, taking into account timing and process aspects. Before treatment, no significant difference was found in SP levels between the two groups (P>0.05). However, after treatment, a significant difference emerged (P<0.05), consistent with findings by Zhu et al., comparing SP level decreases in the SEA and control groups revealed no significant difference (P>0.05), contrasting with Zhu et al., results but aligning with Sjostrom et al., PCA study [7,8]. Therefore, SEA in painless childbirth insignificantly reduces SP levels, warranting further exploration.

NO levels in the SEA and control groups were also investigated, and the researchers found significant differences before and after treatment from both time and process perspectives (p<0.05). Unlike the findings of Chen et al., this study showed significant differences at T0 between groups [9]. In the SEA group, significant differences were observed in NO levels before and after treatment (p<0.05), while no significant differences were noted in the control group (p>0.05). Additionally, the mean decrease in NO levels in both groups was not statistically significant (p>0.05). No significant difference was found in delta NO levels between groups (P>0.05), consistent with pairwise comparisons within both groups (P>0.05). Further research is needed to elucidate the mechanism behind the decrease in NO levels during active labor and SEA's potential role in this reduction.

To see the impact, this study also assessed other dependent variables such as VAS scores, vital signs, APGAR scores, and duration of childbirth. VAS pain level comparisons between SEA and control groups before

treatment yielded non-significant results (P>0.05). However, significant differences were observed at T1 and T2 (P<0.05), suggesting SEA treatment affects VAS scores in both groups. This contrasts with Zhou et al., findings but aligns with Supraptomo and Zhu et al., research, indicating significant changes in VAS scores (P<0.05) [7,10,11].

The main goal of providing analgesia during childbirth is to reduce or eliminate pain. Therefore, VAS, which is a tool to measure pain scale in humans, should reflect lower pain levels in the group receiving SEA compared to the untreated group. The research results further support this theory. According to the theoretical framework, pain triggers the body to interpret tissue ischemia, leading to the release of mediators like NO for vasodilation, TNF-α for enhancing afferent fiber activity, and Substance P for pain signal transmission facilitation. These processes manifest as pain sensations, potentially increasing VAS values. From the study and review conducted, it can be concluded that SEA administration can reduce pain in mothers undergoing normal childbirth.

Vital signs, including blood pressure, pulse, temperature, and respiratory rate, were compared between the SEA and control groups. Significant differences were found for blood pressure, pulse, and respiratory rate (P<0.05), but not for temperature (P>0.05). SEA administration during childbirth impacts blood pressure, pulse, and respiratory rate, but not temperature. This supports Wu et al., findings (P<0.05), contrasting with Chen et al., results (P>0.05) [9,12]. Similarly, Zhou et al., observed no significant temperature changes immediately after treatment (P<0.05), but noted increases later, with higher temperatures in the control group (P>0.05) [10].

Vital signs are essential during neuraxial analgesia in childbirth, given potential side effects like hypotension and apnea. In this Giannubilo et al., study, spinal analgesia was administered to all groups, resulting in nonsignificant changes in vital signs with or without treatment. This study observed that SEA alters blood pressure, respiratory rate, and pulse during childbirth, attributed to vascular resistance reduction by childbirth mediators (NO, progesterone, prostaglandins, etc.,) prompting vital sign alterations [13]. Further research is warranted. In conclusion, SEA during painless childbirth notably impacts blood pressure, pulse, and respiratory rate, but not body temperature.

Further assessment of APGAR scores at 1, 5 and 10 minutes revealed significant differences between the SEA and control groups (P<0.05), aligning with Supraptomo's findings. While SEA administration improves fetal viability, as indicated by enhanced APGAR scores, Zhu et al., observed no significant changes at 1 and 5 minutes between groups (P>0.05). Additionally, significant differences were noted in labor duration between the SEA and control groups (P<0.05). Zhu et al., reported no significant changes during stages I and II (P>0.05) but significant differences during stage III (P>0.05). Conversely, Zhou et al., reported no significant differences during stages I and III (P>0.05) but significant differences during stage II (P<0.05). Supraptomo's study found significant changes during stage I (P<0.05).

The significant difference in labor duration in this study implies that labor with SEA can expedite the process. SEA administration during labor can potentially enhancing vascularization and oxygenation by producing some vasodilators in maternal serum, leading to improved aerobic metabolism, increased ATP production, and stronger uterine contractions, ultimately resulting in faster labor [14,15].

The SEA method using levobupivacaine is currently a popular painless labor technique. Zuarez-Easton et al., state that this method is the primary and most effective approach for labor pain [16]. However, it has an 8.5% failure rate and is associated with drawbacks such as cost, prolonged labor, and potential side effects like intrapartum fever, dural puncture causing pain or scarring, and postpartum headaches. Nevertheless, these side effects have been manageable thus far (Committee on Practice Bulletins-Obstetrics, 2017) [17]. Levobupivacaine is chosen for its lesser motor blockade and lower toxicity, making it the preferred option for painless labor with SEA [18,19]. From this review, it can be concluded that the SEA method using levobupivacaine for painless labor has manageable side effects.

Conclusion

To summarize, SEA using levobupivacaine in painless normal labor provides numerous benefits. It notably decreases TNF-α and substance P levels, though not significantly.

Additionally, it reduces blood NO levels over time and during labor. SEA influences vital signs such as blood pressure, heart rate, and respiratory rate significantly but has no significant impact on body temperature. It boasts minimal side effects compared to regular labor, making it safe. Moreover, it improves infant viability, as indicated by APGAR scores, and reduces pain levels, as reflected in VAS scores. Lastly, SEA significantly shortens labor duration. These findings underscore the effectiveness and safety of SEA with levobupivacaine in painless normal labor, benefiting both mothers and infants.

Conflict of Interest

The authors declare that this study had no external funding resource or any conflict of interests.

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