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Original Article

Effect of Intrathecal Single Dose Clonidine-Bupivacaine - Fentanyl Admixture Versus Bupivacaine - Fentanyl Only on Labour Pain

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Abstract

Objective: To evaluate the effects of clonidine addition to single dose intrathecal bupivacaine-fentanyl admixture on labour pain. ***Design:*** Prospective, randomized, double-blind study. ***Subjects:*** 134 labouring women. ***Methods:*** Following approval, 134 consenting parturients received, intrathecally, either clonidine 25µg, bupivacaine 2.5mg and fentanyl 25µg (group A = 67) or bupivacaine 2.5mg and fentanyl 25 µg (group B = 67). Maternal blood pressure, sensory/motor block, pain, duration of active labour, labour outcome, neonatal APGAR score and umbilical arterial pH were recorded. ***Results:*** Group A rather than B, had longer mean duration and faster onset of effective analgesia (170.0 (20.5) versus 108.7 (19.9) minutes; $P = 0.001$), and (3.6 (1.1) versus 4.9 (0.3) minutes; $P = 0.001$), respectively, and longer time to Bromage 6 ($P = 0.001$). APGAR scores at 1st and 5th minute ($P = 0.16$ and $P = 0.405$ respectively), mean umbilical arterial pH ($P = 0.342$), active labour duration ($P = 0.905$) and labour outcome ($P = 0.052$) were similar. ***Conclusion:*** Compared to group B, group A achieved significantly faster onset, longer duration of effective analgesia and motor block; active labour duration, labour and neonatal outcomes were similar, with minimal side effects.

Keywords: ***Bupivacaine, clonidine, fentanyl, intrathecal labour analgesia.***

Introduction

The pain of labour has been described by most women as the most agonizing experience in their lifetime [1]. Consequently, many women are very anxious about labour, showing intense worries and panics [2]; the provision of sufficient analgesia to decrease labour pain to a tolerable level with minimal side effects, therefore, becomes necessitated. Adequate pain relief entails a number of significant benefits for the parturient and her foetus: (a) maternal psychological distress is replaced with comfort, (b) the attenuation of the stress response results in decreased release of stress hormones whose actions negatively impact the parturient's reserves as well as deprive the foetus of oxygen and nutrients, and (c) decreased endogenous maternal catecholamine levels results in diminution of their inhibitory effects on uterine contractility, prevents maternal acidosis and improves intrapartum maternal well-being [1,3]. Of the various modalities of labour analgesia the use of parenteral opioids and sedatives is the most common, however, it has documented association with neonatal adverse effects [4]. Epidural labour analgesia which is considered gold standard demands high level competence [5], while single-shot spinal analgesia, a technique that is gaining popularity especially in developing countries, has short duration [6]. Besides, neuraxial labour analgesia raises concerns about prolonged second stage and increased instrumental delivery [7]. Owing to the comparatively short duration of action of single-shot intrathecal local anaesthetic, a repeat dose or supplemental analgesia may be required, hence, necessitating local anaesthetic combination with adjuvants to achieve improved quality and longer duration of analgesic effect [6].

The intrathecal co-administration of local anaesthetic and clonidine, an alpha-2 adrenoceptor agonist, increases the duration of postoperative analgesia, sensory and motor block [5]; however, clonidine on its own is not known to provide significant labour analgesia [8]. To achieve excellent labour analgesia using clonidine as sole intrathecal agent would require a high dose that could lead to marked sedation and hypotension [9]. Philippe *et al.*[10], in their study on intrathecal clonidine combined with sufentanil for labour analgesia, in 98 parturients, concluded that the administration of 30µg intrathecal clonidine combined with 2.5µg or 5µg intrathecal sufentanil significantly increased the duration of analgesia, during the early first stage of labour, without adverse maternal or foetal effects, but did not determine the efficacy of this combination on advanced labour. The impact of clonidine on intrathecal bupivacaine and fentanyl mixture is yet to be sufficiently evaluated especially in

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our sub-region, therefore, this study aimed to evaluate the effects of intrathecal clonidine (25µg) on intrathecal labour analgesia from a mixture of 2.5mg bupivacaine and 25µg fentanyl.

Materials and Method

Institutional ethical approval was secured from the Research and Ethics Committee of the University of Port Harcourt Teaching Hospital, for a prospective, randomized, double blind, comparative cohort study in 134 labouring women. All subjects consented and completed the study which was conducted from January 2023 to May 2023, in the University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers state, Nigeria.

Sample Size Determination

Sample (n) size was calculated using power analysis formula for comparative study [11]:

$$n = \frac{2(Z_\alpha + Z_\beta)^2 [(\sigma_1)^2 + (\sigma_2)^2]}{(\mu_1 - \mu_2)^2}$$

Where

n = minimum sample size,

Z_α = 0.84 using power of 80% for this study; Z_β = 1.96 at 5% significance level,

σ_1 = standard deviation of group 1 and σ_2 = standard deviation of group 2.

In a related mini review by Lugo *et al*.[12], the group that received intrathecal clonidine and bupivacaine (Group 1) had a mean effective analgesic duration of 275.10±96.09 minutes, while the mean duration of effective analgesia was 211.73±74.80 minutes in the group which received bupivacaine alone (Group 2).

Substituting:

$$n = \frac{2 \times (0.84 + 1.96)^2 [(96.09)^2 + (74.80)^2]}{(275.10 - 211.73)^2}$$

n = 28.95, approximately 58 per group.

Accommodating 10% attrition, the sample size was increased to 134 subjects for the two groups.

Randomization and Blinding

Patients were assigned to two groups (A and B), each consisting of 67 subjects, by simple randomization ensured via recruitment of trained Research Assistants. Eligible subjects, under the supervision of a Registrar Anaesthetist (first Research Assistant), were directed to pick one from a bag containing 134 opaque envelopes, concealing alphabets A and B in an equal ratio of 67; this was carried out in the labour ward reception following confirmation of labour by the attending Obstetrician. The Research Assistatnt wrote the patient's name on the envelope picked before it was opened, allocated the patient to that group designated by the alphabet picked, and excluded the envelope from the rest. The study agents were prepared by a blinded Senior Registrar Anaesthetist (second Research Assistant) who also assigned a different code against each subject's group and hospital number, while the Lead investigator, blinded to the group allocations and drug preparations, administered the study agents, assessed the patient outcomes and recorded the parameters. The labour ward nurse kept the codes for rapid access to any subjects in the event of any adverse effect.

Inclusion and Exclusion Criteria

Women presenting to the University of Port Harcourt Teaching Hospital in first stage labour, belonging to class II of the American Society of Anesthesiologists physical status classification, with singleton foetus in vertex presentation and longitudinal lie, who attained 5cm cervical dilatation, with no obstetric complication comprised the inclusion criteria, while age <18years, presence of pre-existing or pregnancy-induced hypertension, multiple gestation, obesity (BMI >30kg/m^2), height <1.53metres, endocrine diseases, diagnosed foetal anomalies, contra-indication to central neuroaxial block, contraindication to vaginal delivery, positive history of allergy to study agents, inability to communicate, failure to locate the intrathecal space after two attempts, current opioid medication, current sedative medication, and refusal to participate in the study constituted the exclusion criteria.

Conduct of the Study

At the labour ward, multiparameter monitor (DASH 4000 USA) was attached for baseline and continuous recording of maternal pulse rate, blood pressure and arterial haemoglobin Oxygen saturation (SpO_2) while uterine contractions and foetal heart rate monitoring were done via a cardiotocograph strapped to the maternal abdomen. At attainment of 5cm cervical dilatation, subjects received 500ml of lactated Ringer's solution intravenously, via a 16-gauge cannula over 5 - 10 minutes and a two-puncture combined spinal epidural (CSE) technique was performed at the L3/L4 intervertebral level, aseptically, while the patient was supported in the sitting position. Following skin and subcutaneous infiltration with 2ml of lidocaine 1%, the epidural space was located first by loss-of-resistance-to-saline technique, using an 18-gauge Tuohy needle, through which 3cm of 20-gauge epidural catheter was advanced beyond the needle tip, without being activated. After confirmation of correct catheter placement by negative aspiration test to blood and cerebrospinal fluid, and by non-detection of ≥15% increase in pulse rate from baseline value, on injection of 3ml of lidocaine 1.5% containing epinephrine 5µg/ml, a 26-gauge Whitacre-point spinal needle was advanced through a 21-gauge hypodermic needle-introducer, into the intrathecal space at same intervertebral level; the study solution appropriate for the patient's group was then administered intrathecally, the puncture site was covered with sterile dressing and the parturient returned quickly to the supine position, with 15 – 30^o head-up and left lateral uterine displacement. Accordingly, subjects received, intrathecally, 2ml of study solution made up of either 25µg clonidine plus heavy bupivacaine 2.5mg and 25µg fentanyl (group A), or 2.5mg bupivacaine and 25µg fentanyl only (group B).

Maternal hypotension in this study was defined as systolic blood pressure (SBP) < 100 mmHg or a 20% decrease from baseline value, and maternal bradycardia as pulse rate less than 60 beats /minute; arterial desaturation (SpO_2 <94% on room air) was treated with supplemental Oxygen administered via simple face mask at a flow rate of 4 to 5 litres per minute. Sensory block was assessed using cotton wool soaked in ethyl alcohol in a cranio-caudal direction bilaterally; the time to onset as well as to maximum sensory block height was noted. Motor block was evaluated using the Bromage score as modified by Breen *et al*.[13]: [complete block (unable to move feet or knees) = 1; almost complete block (able to move feet only) = 2; partial block (just able to move knees) = 3; detectable weakness of hip flexion while supine (full flexion of knees) = 4; no detectable weakness of hip flexion while supine = 5; able to perform partial knee bend = 6]. A 10cm visual analogue scale (VAS) previously explained to the subjects was used for pain assessment. Pain, sensory and motor block assessments were done every 5 minutes for the first 15 minutes, then at 15 minutes interval for 1 hour, and subsequently every half hour till 30 minutes postpartum.

When patient requested analgesic or at VAS score ≥4, supplemental 10ml analgesic bolus comprising epidural plain bupivacaine (Duracaine, Myungmoon Pharm) 0.1% (9ml) and 1ml of 25µg fentanyl (Panapharma) was administered, and the total number of doses recorded. The onset of effective analgesia was defined as the time from intrathecal injection to VAS score ≤ 3 cm, and the duration of effective analgesia as the time from the onset of effective analgesia to first request for analgesic or VAS score ≥ 4cm. Level of sedation in the parturients was monitored using Ramsay sedation scale [14]**:** [awake, anxious and agitated or restless = 1; awake, co-operative, oriented and tranquil = 2; awake, responds to command only = 3; asleep, brisk response to glabellar tap or loud noise = 4; asleep, sluggish response to glabellar tap or loud noise = 5; asleep, no response to glabellar tap or loud noise = 6]. Neonatal APGAR scoring was done at 1 and at 5 minutes of birth; umbilical cord arterial blood pH was determined using a pH meter (IQ Scientific Instruments, Minilab Model IQ 125 USA). The subjects were also monitored for assisted instrumental vaginal delivery, Caesarean, as well as for the occurrence of any adverse effects such as maternal respiratory depression, nausea, vomiting, pruritus, hypotension, bradycardia, foetal heart abnormality, postpartum urinary retention and promptly treated. Maternal satisfaction was assessed using 5-point Likert scale [15]: [1 = very poor, 2=poor, 3 = good, 4 = very good, 5 = excellent].

Data collection and Analysis

All data was entered on a spreadsheet and analyzed using the Statistical Product and Service Solutions (SPSS) version 25 (IBM, Chicago, IL, USA) software for statistical analysis, by a statistician. Statistical significance was set at $P < 0.05$.

Results

The socio-demographic characteristics of the subjects were comparable in terms of their mean age in years [30.3 (4.2) versus 30.7 (4.8), $P = 0.579$), age distribution ($P = 0.912$), BMI in kg/m^2 ($P = 0.723$), parity ($P = 0.277$), level of education ($P = 0.548$), and in the distribution of their ethnic nationalities ($P = 0.675$), across the two groups **(Table I).**

There was significantly longer **mean analgesic duration** (minutes) noted in group A compared to group B, $P = 0.001$; also, the mean analgesic duration (minutes) observed in the primiparous ($P = 0.001$), multiparous ($P = 0.001$) and grandmultiparous ($P = 0.001$) sub-categories, were significantly greater in group A in comparison to group B. Relative to group B, the **onset of effective analgesia** was significantly faster in group A ($P = 0.001$); as well, the values showed significantly faster analgesic onset amongst the subcategories of subjects in group A: $P = 0.001$ for the primiparous, P=0.001 for the multiparous, and $P = 0.007$ for the grandmultiparous. The **time (minutes) taken to achieve maximum level of sensory block** was comparable between the two groups ($P = 0.516$); however, the **maximum level of sensory block** (T4) in group A was significantly higher compared to T6 in group B, $P = 0.001$. Subjects in group A recorded significantly lower total median **number of supplemental epidural analgesic consumption**, compared to subjects in group B, the difference being also statistically significant, $P = 0.046$ **(Table II)**.

Best ambulation (Modified Bromage 6) was achieved significantly faster in group B compared to group A ($P = 0.001$), the observation occurring at 60 minutes post study drug administration. Consistently, there was significantly greater attainment of best ambulation in group B relative to group A at the 90th, 120th and 150th minute, $P = 0.001$, 0.001 and 0.001 respectively. Although longer in group A, the mean duration of active phase of labour was not statistically different, $P = 0.905$. More women had vaginal delivery than Caesarean and the proportion of vaginal delivery in the two groups was comparable, $P = 0.052$ **(Table III)**.

The mean gestational ages (weeks) at delivery ($P = 0.102$), and the mean birth weights (kg) of the newborns ($P = 0.291$), in groups A and B were statistically comparable. As observed, the neonatal outcomes in the two group, evidenced by the median APGAR Scores at 1 minute and at 5 minutes ($P = 0.16$ and $P = 0.405$ respectively), as well as by the mean umbilical cord arterial pH values ($P = 0.342$) were also statistically similar **(Table IV)**.

While adverse effects such as hypotension ($P = 0.001$), drowsiness ($P = 0.001$) and nausea ($P = 0.042$) had significantly greater occurrence in group A than in group B, the occurrence of difficult micturition (P =0.053), pruritus (P=0.161), bradycardia ($P = 0.649$) and respiratory depression ($P = 1.000$) was comparable across the two groups **(Table V)**. Also, there was statistical similarity ($P = 0.705$) in maternal satisfaction, which was rated as excellent by the subjects enrolled in this study.

Table I: Socio-demographic characteristics and parity of parturients.

Characteristics		**Study Group**		**Statistical test (p-Value)**
	Total N = 134	**Group A N = 67**	**Group B N = 67**	
Age group	**N (%)**	**N (%)**	**N (%)**	
20 - 24 years	14 (10.4)	8 (11.9)	6 (9.0)	0.53[a] (0.912)
25 - 29 years	43 (32.1)	20 (29.9)	23 (34.3)	
30 - 34 years	48 (35.8)	24 (35.8)	24 (35.8)	
35 - 39 years	29 (21.6)	15 (22.4)	14 (20.9)	
Age in years – Mean (SD)	**30.5 (4.5)**	**30.3 (4.2)**	**30.7 (4.8)**	0.56[b] (0.579)
Educational status	**N (%)**	**N (%)**	**N (%)**	
Primary	6 (4.5)	2 (3.0)	4 (6.0)	1.20[c] (0.548)
Secondary	10 (7.5)	4 (6.0)	6 (9.0)	
Tertiary	118 (88.1)	61 (91.0)	57 (85.1)	
Occupation	**N (%)**	**N (%)**	**N (%)**	
Civil servant	67 (50.0)	35 (52.2)	32 (47.8)	2.20[a] (0.333)
Business/Trader	53 (39.6)	23 (34.3)	30 (44.8)	
Unemployed	14 (10.4)	9 (13.4)	5 (7.5)	

Tribe	**N (%)**	**N (%)**	**N (%)**	
Igbo	64 (47.8)	32 (47.8)	32 (47.8)	2.44[c] (0.675)
Ikwerre	37 (27.6)	21 (31.2)	16 (23.9)	
Ijaw	17 (12.7)	6 (9.0)	11 (16.3)	
Yoruba	11 (8.2)	5 (7.5)	6 (9.0)	
Others	5 (3.7)	3 (4.5)	2 (3.0)	
Parity groups	**N (%)**	**N (%)**	**N (%)**	
Primiparous (Para 1)	60 (44.8)	34 (50.7)	26 (38.8)	1.94[c] (0.379)
Multiparous (Para 2 – 4)	67 (50.0)	30 (44.8)	37 (55.2)	
Grandmultiparous (Para ≥ 5)	7 (5.2)	3 (4.5)	4 (6.0)	
Parity – Median (Range)	**2 (1 – 6)**	**1 (1 – 5)**	**2 (1 – 6)**	2014.0[d] (0.277)
Anthropometry	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Weight in kg – Mean (SD)	81.1 (8.9)	81.4 (8.7)	80.8 (9.2)	0.35[b] (0.728)
Height in m – Mean (SD)	1.6 (0.1)	1.7 (0.1)	1.6 (0.1)	1.02[b] (0.308)
BMI in kg/m^2 – Mean (SD)	29.8 (2.6)	29.7 (2.3)	29.9 (2.9)	0.36[b] (0.723)

a = Chi-square test; b = Student's t-test; c = Fisher's exact test; d = Mann Whitney U test; BMI = Body mass index; SD = Standard deviation

Table II: Onset and duration of analgesia, sensory block onset and height, pain scores, and total supplemental epidural analgesic consumption.

Characteristics		**Study Group**		**Student's t-test (p-Value)**
	Total N = 134 Mean (SD)	**Group A N = 67 Mean (SD)**	**Group B N = 67 Mean (SD)**	
Time to onset of effective analgesia in minutes				
Total population	4.3 (1.0)	3.6 (1.1)	4.9 (0.3)	8.66 (0.001*)
Primiparous women	4.2 (1.2)	3.6 (1.2)	4.9 (0.3)	5.41 (0.001*)
Multiparous women	4.4 (0.9)	3.8 (1.0)	4.9 (0.3)	6.25 (0.001*)
Grandmultiparous women	3.9 (0.9)	3.0 (0.1)	4.5 (0.6)	4.39 (0.007*)
Duration of effective analgesia in minutes				
Total population	139.4 (36.8)	170.0 (20.5)	108.7 (19.9)	17.29 (0.001*)
Primiparous women	145.6 (40.2)	178.4 (16.5)	105.2 (16.2)	16.92 (0.001*)
Multiparous women	133.1 (33.3)	160.0 (21.0)	110.1 (23.0)	9.09 (0.001*)
Grandmultiparous women	145.7 (32.1)	174.5 (22.8)	120.0 (14.8)	16.41 (0.001*)
Time to attain maximum level of sensory block in minutes	11.5 (4.2)	11.2 (3.4)	11.7 (4.9)	0.65 (0.516)
Maximum level of sensory block – Median (Range)	T6 (T4 - T8)	T4 (T4 - T 8)	T6 (T4 - T8)	465.0[a] (0.001*)
Pain score before activation of epidural - Median (Range)	5.0 (4.0 - 10.0)	5.0 (4.0 - 10.0)	5.0 (4.0 - 10.0)	1214.5[a] (0.164)
Total number of epidural doses given - Median (Range)	2.0 (0.0 - 10.0)	2.0 (0.0 - 10.0)	3.0 (0.0 - 10.0)	1181.5[a] (0.046*)

**Statistically significant; [a]Mann-Whitney U test; N = number; SD = Standard deviation*

Table III: Modified Bromage score, duration of active phase of labour and mode of delivery.

Characteristics		**Study Group**		**Fisher's exact (p-Value)**
	Total N (%) N = 134	**Group A N (%) N = 67**	**Group B N (%) N = 67**	
Modified Bromage score at 30 mins				
4 to 5	14 (10.4)	0 (0.0)	14 (20.9)	41.56 (0.001*)
2 to 3	59 (44.0)	19 (28.4)	40 (59.7)	
1	61 (45.5)	48 (71.6)	13 (19.4)	
Modified Bromage score at 60 mins				
6	10 (7.5)	0 (0.0)	10 (14.9)	40.35 (0.001*)
4 to 5	59 (44.0)	17 (25.4)	42 (62.7)	

2 to 3	61 (45.5)	46 (68.7)	15 (22.4)	
1	4 (3.0)	4 (6.0)	0 (0.0)	
Modified Bromage score at 90 mins				
6	56 (41.8)	8 (11.9)	48 (71.6)	51.01 (0.001*)
4 to 5	59 (44.0)	42 (62.7)	17 (25.4)	
2 to 3	19 (14.2)	17 (25.4)	2 (3.0)	
Modified Bromage score at 120 mins				
6	85 (63.4)	25 (37.3)	60 (89.6)	22.86 (0.001*)
4 to 5	45 (33.6)	40 (59.7)	5 (7.5)	
2 to 3	4 (3.0)	2 (3.0)	2 (3.0)	
Modified Bromage score at 150 mins				
6	117 (87.3)	52 (77.6)	65 (97.0)	11.30 (0.001*)
4 to 5	17 (12.7)	15 (22.4)	2 (3.0)	
Caesarean	20 (14.9)	6 (9.0)	14 (20.9)	
Vaginal Delivery	114 (85.1)	61 (91.0)	53 (79.1)	(0.052.)
		Mean (SD)	**Mean (SD)**	
Duration of active labour (hours)		4.5 (1.6)	4.4 (2.1)	(0.905)[b]

Data are expressed as number (N), percent (%), mean (SD); SD = Standard deviation
**Statistically significant*; b = *t-test P*-value.

Table IV: Immediate Neonatal outcomes (APGAR scores and umbilical cord blood pH) in the two groups.

Characteristics		**Study Group**		**Statistical test (p-Value)**
	Total N = 134	**Group A N = 67**	**Group B N = 67**	
Sex	**N (%)**	**N (%)**	**N (%)**	
Male	60 (44.8)	28 (35.8)	32 (47.8)	0.48[a] (0.489)
Female	74 (55.2)	39 (64.2)	35 (52.2)	
APGAR Score at 1 minute	**N (%)**	**N (%)**	**N (%)**	
Good APGAR (≥ 7)	126 (94.0)	65 (97.0)	61 (91.0)	2.22[c] (0.274)
Poor APGAR (< 7)	8 (6.0)	2 (3.0)	6 (9.0)	
APGAR Score at 1 minute – Median (Range)	8 (3 – 9)	8 (4 – 9)	8 (3 – 9)	2110.5[d] (0.146)
APGAR Score at 5 minutes	**N (%)**	**N (%)**	**N (%)**	
Good APGAR (≥ 7)	128 (95.5)	65 (97.0)	63 (94.0)	0.71[c] (0.680)
Poor APGAR (< 7)	6 (4.5)	2 (3.0)	4 (6.0)	
APGAR Score at 5 minutes – Median (Range)	9 (5 – 10)	9 (5 – 10)	9 (5 – 10)	2177.5[d] (0.405)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Umbilical cord arterial pH	7.2 (0.1)	7.2 (0.1)	7.2 (0.2)	0.95[b] (0.342)
Birth Weight	3.19 (0.48)	3.18 (0.46)	3.21 (0.49)	1.06[b] (0.291)
Gestational age in weeks	39.1 (1.2)	38.9 (1.3)	39.3 (1.1)	1.65[b] (0.102)
Foetal heart rate	142.0 (3.8)	141.4 (3.1)	142.7 (4.3)	1.93[b] (0.056)

Data are expressed as number (N), percent (%); SD = Standard deviation
[a]Chi-square test; [b]Student's t –test; [c]Fisher's exact; [d]Mann Whitney U test

Table V: Occurrence of adverse effects and maternal satisfaction in the groups.

Characteristics		**Study Group**		**Statistical test (p-Value)**
	Total N (%) N = 134	**Group A N (%) N = 67**	**Group B N (%) N = 67**	
Hypotension				
Absent	88 (65.7)	24 (35.8)	64 (95.5)	61.12[a]
Mild	39 (29.1)	37 (55.2)	2 (3.0)	(0.001*)
Disturbing	7 (5.2)	6 (9.0)	1 (1.5)	
Difficult micturition				

Absent Mild Disturbing	121 (90.3) 9 (6.7) 4 (3.0)	63 (94.0) 4 (6.0) 0 (0.0)	58 (86.6) 5 (7.4) 4 (6.0)	5.86[a] (0.053)
Pruritus				
Present	78 (58.2)	43 (64.2)	35 (52.2)	1.96[b] (0.161)
Absent	56 (41.8)	24 (35.8)	32 (47.8)	
Drowsiness				
Present	54 (40.3)	47 (70.1)	7 (10.4)	49.63[b] (0.001*)
Absent	80 (59.7)	20 (29.9)	60 (89.6)	
Bradycardia				
Present	5 (3.7)	3 (4.5)	2 (3.0)	0.21[a] (0.649)
Absent	129 (96.3)	64 (95.5)	65 (97.0)	
Respiratory depression				
Present	4 (3.0)	2 (3.0)	2 (3.0)	0.00[a] (1.000)
Absent	130 (97.0)	65 (97.0)	65 (97.0)	
Nausea				
Present	4 (3.0)	0 (0.0)	4 (6.0)	4.12[a] (0.042*)
Absent	130 (97.0)	67 (100.0)	63 (94.0)	
Maternal satisfaction	124 (92.5)	63 (94%)	61 (91%)	0.70[b] (0.705)

Data are expressed as number (N), percent (%)
*[a]Fisher's exact; [b]Chi-square test; *Statistically significant*

Discussion

Amongst parturients with comparable socio-demographic features, the intrathecal administration of 25µg clonidine added to 2.5mg hyperbaric bupivacaine and 25µg fentanyl admixture in group A, demonstrated a significantly longer mean duration and faster mean onset time of effective labour analgesia, a greater maximum height of sensory block and longer duration of motor block, with associated higher occurrence of mild to moderate hypotension, drowsiness and nausea than intrathecal 2.5mg bupivacaine and 25µg fentanyl admixture only. However, the mean duration of active phase of labour, neonatal outcomes and maternal satisfaction were comparable between the two groups.

The analgesic efficacy and safety of intrathecal alpha$_2$ agonists such as clonidine, in combination with bupivacaine for Caesarean and vaginal deliveries had been reported [6,16,17]; its analgesic properties have been linked to activation of α_2 receptors located in the dorsal horn, which mediate inhibition of presynaptic neurotransmitter release and postsynaptic afferent nociceptive signal transmission through hyperpolarisation [18]. There was significantly longer duration of analgesia observed in this study in group A, attributable to the occurrence of pharmacological synergism between clonidine and fentanyl administered intrathecally in same parturient, which was absent in group B. This fact most likely underpins the observed differences between the two groups in this study. That the co-administration of opioid-alpha$_2$-adrenoceptor agonist results in analgesic synergism had been documented by Chabot-Doré *et al.*[19], and agrees with the findings by Hao *et al.*[20]. Following isobolographic analysis Ossipov *et al.*[21] reported that the observed synergism did occur at the spinal level; also, from electrophysiology, Stone *et al.*[22] demonstrated that the alpha$_2$-opioid agonist synergism was confined almost exclusively to a spinal level pharmacological interaction. Consistently, the mean duration of effective analgesia in the primiparous, multiparous and grand multiparous sub-categories was significantly longer in group A relative to B, corroborating the empirical reports by Chiari *et al.*[23] and Mercier *et al.*[24], and supporting Sia *et al.*[25], with a corresponding significantly faster onset, depicting an opioid-alpha$_2$ agonist synergism without limitation to parity. The observation lends support to the documentation in a similar study by Galante [26], as well as by Fyneface-Ogan *et al.*[3]. Consequently, parturients in group A, relative to B, consumed significantly less supplemental epidural analgesic ($P = 0.046$).

The median maximum sensory block height was significantly greater in group A (T4), with associated longer motor block, compared to B (T6), indicating greater cephalad drug spread within the subarachnoid space in group A. Similarly higher (T2) sensory block level in association with intrathecal clonidine had also been reported in earlier studies [24,27]. Again, an α_2-opioid synergism enhancing greater local anaesthetic motor block density, coupled with induced vasoconstriction delaying drug absorption from the site of action might account for the observed significantly longer motor block in group A. This observation is also consistent with those of previous studies [28,29].

The comparability of neonatal outcomes is consistent with earlier reports on the effect of clonidine exclusion with its addition to medications for labour analgesia [9,30]. Also, Allen *et al.*[17] similarly documented the absence of negative impact by clonidine on neonatal APGAR scores or umbilical cord artery pH, compared to control.

As observed, the mean durations of active phase of labour across the sub-categories of parturients were statistically similar in the two groups; this, together with the comparably greater vaginal than Caesarean births, could be conveying an important fact. A successful outcome of normal labour is the product of favourable interplay between the maternal uterine forces, maternal pelvic

dimensions and the foetus. An optimal tone in the pelvic floor muscles, together with their anatomical slope, flexibility and stretchability ensures a favourable mechanism of foetal descent and rotation through the maternal pelvis during labour, resulting in an eventual occipito-anterior position. Eventually, foetal expulsion is enhanced by physiological reflexes [31] - **Ferguson reflex** (a neuroendocrine reflex causing oxytocin surge) and **foetus ejection reflex** (involuntary, powerful, expulsive contractions) - plus maternal voluntary bearing down effort, enabled by optimal abdominal wall muscle tone. In this regard, the traditional epidural bupivacaine 0.25% has been associated with prolonged labour and increased rate of instrumental vaginal delivery [32]; this is attributable to the consequent impairment of motor function in anterior abdominal wall and pelvic floor muscles, by a dense neuroaxial blockade [33]. Therefore, inferentially, there was absence of impairment by intrathecal 2.5mg bupivacaine-25µg fentanyl admixture with or without clonidine, of the uterine vectors, pelvic floor muscle tone, the physiological reflexes and maternal voluntary effort considered to be of critical significance in the mechanisms of active phase labour. This, also, is consistent with the findings from another study which reported a statistical similarity in the modes of delivery between clonidine-treated and clonidine-untreated groups [27]. Of note, several research studies have demonstrated an existing direct relationship between the concentration of local anaesthetic used for neuraxial labour analgesia and rate of instrumental/operative delivery. James *et al.*[34], analyzing the effect of different concentrations of bolus bupivacaine for epidural labour analgesia, documented a lower incidence of instrumental vaginal delivery in the group of women who were assigned to receive bupivacaine 0.1% with fentanyl 2µg/ml, than the group which received 0.25% bupivacaine (6% versus 24%, $P = 0.03$). In a larger randomized study, Olofsson *et al.*[35] similarly observed that women who received a 'high-dose' 0.25% epidural bupivacaine with epinephrine had a higher instrumental vaginal delivery, in comparison with those who were given a 'low-dose' 0.125% bupivacaine with sufentanil. Also, Fyneface-Ogan *et al.*[36], in their study of the impact of neuraxial versus parenteral opioid-**sedative labour analgesia in 50 labouring women, observed** that the rate of Caesarean delivery between the group that received hourly 10ml epidural 0.125% bupivacaine (32% [8/25]) and the one that had intravenous pentazocine-promethazine (44% [11/25]), had no statistical difference (OR 0.60; 95% CI, 0.19-1.90), showing a beneficial association of low-dose bupivacaine with absence of significant motor impairment and low Caesarean/instrumental vaginal delivery rate during the conduct of neuraxial labour analgesia.

Again, in their prospective study of the effect of single intrathecal 2.5mg bupivacaine combined with 25µg fentanyl plus 250µg morphine versus control on mother, foetus and labour outcome, Chauhan *et al.*[37] reported no statistical difference between the two groups in number of Caesarean in the first stage ($P = 0.886$), and mean duration of second stage of labour ($P = 0.359$). The authors [37] also noted that a moderate to severe motor weakness in the lower limbs occurred in the intrathecal analgesia group, in 98% of the subjects at the 5th minute, but decreased to 0% at the 30th minute, following intrathecal block, with an associated mean duration of analgesia of 248.96±23.505 minutes and a mean duration of labour of 244.75±20.300 minutes. On a critical analysis of this latter observation by Chauhan *et al.*[37], low dose intrathecal bupivacaine, while achieving a relatively longer analgesic duration, is associated with a rapid onset of dense motor block that is relatively rather short-lived; consequently, similar to the use of low dose epidural bupivacaine for labour analgesia, there was absence of lasting significant decrease in abdominal and pelvic floor muscle tone, following low dose intrathecal block for labour analgesia in the parturients. In the present study, with the addition of 25µg fentanyl alone (group B) or 25µg clonidine plus 25µg fentanyl (group A) to 2.5mg bupivacaine intrathecally, only 17 (25.4%) in group A and 2 (3%) in group B had moderate motor impairment at 90 minutes post block, revealing a shorter duration of motor blockade than the corresponding duration of active phase of labour [4.5 (1.6) and 4.4 (2.1) hours] observed in the groups; this agrees with the finding by Chauhan *et al.* [37].

Pruritus occurred most commonly, without significant difference between the groups, and similar occurrence had been reported in related studies on clonidine [27,30,38,39]. Importantly, drowsiness and hypotension were significantly more common in group A than in group B, and this supports findings of other authors reporting about clonidine medications [9,24,25,40]. Another study [41] also reported greater decrease in mean arterial pressure amongst clonidine-treated patients, compared to the clonidine-untreated (25 +/- 10% vs 15 +/- 12%, $P < 0.05$). Inferentially, in group A relative to B in this study, there was positive association of greater height of autonomic neuronal blockade with higher maximum sensory block height. Nausea and difficult micturition were significantly more common in group B; this might be underpinned by an absence of alpa2 agonism in this group, allowing unopposed opioid-related effects. Maternal satisfaction with childbirth was excellent and comparable between the groups, attributable mainly to adequate labour analgesia, and this lends support to the documentation by Kuczkowski *et al.* [42].

In conclusion, the pain relief characteristics of 25µg clonidine addition to 2.5mg heavy bupivacaine-25µg fentanyl admixture for single-shot spinal analgesia in labour, were superior to those demonstrated by 2.5mg heavy bupivacaine-25µg fentanyl alone, evidenced by significantly faster onset and longer duration of effective analgesia, higher sensory block level, and correlating significantly longer motor block, without negatively impacting active labour duration, labour and neonatal outcome; maternal satisfaction was similarly excellent, with minimal adverse effects.

Declarations

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Conflict of interest

None

Ethical approval

Granted by the University of Port Harcourt Teaching Hospital Research Ethics Committee (Ethical Clearance Reference: UPTH/ADM/90/S.II/VOL.XI/1266)

Authors' Roles

CO: Data acquisition, initial intellectual content development and principal investigating author

ATA: Manuscript preparation, final intellectual content development and corresponding author.
OKI: Data interpretation, manuscript integrity appraisal and critical reviewing author.
SFO: Initial study conception, study design, and final version approving author.

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