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Incidence of hypotension in lower segment Caesarean section - a comparison of intrathecal Fentanyl-Bupivacaine combination with Bupivacaine alone

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ABSTRACT

Introduction: After subarachnoid block with conventional heavy Bupivacaine, hypotension is the most common complication and is caused by decrease in systemic vascular resistance and/or cardiac output. Even with standard doses of the drug for parturient, there are evidences of severe hypotension and other complications despite adequate analgesia and anaesthesia. Adjuvants are used to enhance the quality of blocks with less complications.

Objectives: It was to evaluate the effectiveness of combining bupivacaine and fentanyl for spinal anesthesia during lower segment Caesarean section (LSCS) as opposed to using bupivacaine alone for the incidence of hypotension.

Methodology: This is a prospective study of 210 patients aged 18-35 years of American society of Anesthesiologists Physical Status II undergoing elective lower segment Caesarean section, randomly assigned to two groups: Group A, received a mixture of intrathecal 2ml of 0.5% Bupivacaine and 10 mcg Fentanyl(2.2ml) and Group B, received only 2.2 ml of Bupivacaine. Noninvasive blood pressure was checked at 1,2,4,6,10,20,40 and 60 min after subarachnoid block and then post-surgery.

Results: The occurrence of hypotension was higher in Group B (26.6%) compared to Group A (8.6%).

Conclusion: Our study suggests that the intrathecal Fentanyl-Bupivacaine combination is effective in reducing the incidence of hypotension after SAB for elective LSCS. Additional research is needed to determine this combination's optimal dosage and timing.

INTRODUCTION

During lower segment caesarean section (LSCS) surgeries, it is common for patients to experience a significant drop in blood pressure (systolic blood pressure <90 mmHg), a condition known as hypotension¹. Research has shown that as many as 60% to 80% of LSCS patients may be affected by hypotension due to the vasodilating effects of spinal anesthesia². Healthcare professionals carefully monitor patients undergoing LSCS to promptly detect and address hypotension to avoid any complications for both the mother and the baby.

Every year, around 15 million spinal anesthesia procedures are performed worldwide³. The choice of anesthesia is influenced by factors such as the specific surgery's requirements, the patient's personal preferences, and the skill level of the anesthesiologist. Anesthesiologists have a range of options at their disposal for intrathecal use, including bupivacaine, hyperbaric bupivacaine, ropivacaine, and

levobupivacaine^{4,5}. Bupivacaine, a type of local anesthetic known as an amide, is highly potent with a slow onset and long-lasting effects. For cesarean sections, the recommended intrathecal dose of hyperbaric bupivacaine ranges from 12 to 15 mg⁵. During cesarean deliveries, there is often manipulation of the peritoneum and intraperitoneal organs, leading to intraoperative visceral pain. By using high doses of hyperbaric bupivacaine, the occurrence of intraoperative visceral pain can be minimized⁶. However, administering spinal anesthesia during a cesarean section continues to be a difficult task for anesthetists due to the risk of severe low blood pressure caused by high doses of bupivacaine or the potential for inadequate anesthesia from low doses of bupivacaine.

A recent thorough review and analysis of ten randomized trials revealed that mothers who were administered a combination of low-dose bupivacaine and fentanyl had a lower risk of experiencing hypotension compared to those who were given traditional doses of bupivacaine alone⁷. The results showed a significant reduction in the incidence of hypotension with the combined approach. Fentanyl stands out among synthetic opioids for its increased strength, quick onset of effects, and rapid distribution throughout the body. This leads to a decrease in the drug's concentration in the blood, ultimately improving pain relief following surgery⁸. Given the above, the purpose of the study is to compare the incidence of hypotension between intrathecal Fentanyl-Bupivacaine combination and Bupivacaine alone.

METHODOLOGY

A prospective randomized double-blind study was done in the operating theatre of the obstetric department at Nobel Medical College Teaching Hospital from February 2023 to February 2024. After approval from the institutional review committee, IRC-NMCTH/735/2023 dated February 01, 2023, informed consent was obtained from the patients before the study and written consent was collected from women with ASA PS II, who were between 18-35 years old and had a normal, uncomplicated pregnancy. Parturient scheduled for an elective cesarean section and willing to participate in the study were included. Randomly allocated two distinct groups using sealed envelope technique were formed for the study. The sample size was calculated by using standard protocol and previous study⁹. Sample size $(n) = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \cdot SD^2}{d^2}$ Where, SD (standard deviation = 2.52 as per previous study⁹) and desirable error $(d)=1$, Confidence interval 95% CI =0.84, and the power of test at 80%. The final calculated sample size is 49.14, thus taken as 50 in each group. But, from a statistical perspective, we gathered a total of 105 participants per group. After obtaining approval from the institutional ethics committee and receiving written informed consent, 105 patients were recruited in both groups for the study.

Exclusion criteria for this study included women experiencing complicated pregnancies involving conditions like preeclampsia, pregnancy-induced hypertension, gestational diabetes, abnormal placenta (placenta previa), multiple pregnancies, body mass index outside the range of 22 to 35, significant systemic

diseases (such as heart, kidney, or liver conditions), those in need of emergency C-sections, individuals with allergies to the medications being used in the study, and those opting out of regional anesthesia.

After pre-anaesthetic checkup, all patients were explained about the anaesthetic plan and premedication was prescribed. Standard protocol of NPO of 8 hours was maintained. After arrival in the operating room, an intravenous access with an 18 G cannula was secured in the non-dominant hand and a balanced solution was infused at a rate of 20ml/kg. Standard monitoring was achieved with baseline heart rate, non-invasive blood pressure, oxygen saturation and ECG recordings. An anesthesiologist and a resident doctor were chosen to gather the data and received comprehensive training for a day on effective data collection techniques. In addition, another doctor was tasked with supporting and overseeing the data collection process. The resident doctor was blinded to the procedure and using sealed envelope technique he divided the patients into two groups, group A and group B. Under all aseptic precautions, spinal anesthesia was performed in sitting position with 25 G Quincke spinal needle at L2-3/L3-4 interspace. After obtaining free flow of CSF, Group A received 2 ml of hyperbaric bupivacaine 0.5% with 10 mcg fentanyl (0.2 ml) with total volume 2.2 ml while group B received 0.5% hyperbaric bupivacaine (2.2 ml). After the procedure, the patients were turned supine with a slight tilt to the left side. Sensory block was confirmed with an alcohol swab until reaching T6. The extent of the motor block was evaluated using the modified Bromage scale (0=able to move hip, knee and ankle; 1=unable to move hip but able to move knee and ankle; 2=unable to move hip and knee and but able to move ankle; 3=unable to move hip, knee and ankle)¹⁰. Surgery commenced once the sensation block reached the T6 level or higher.

After spinal anaesthesia, blood pressure was recorded every 2 min for first 10 minutes then till the end of surgery blood pressure was recorded for every 5 min. Fall in blood pressure below 25% of baseline was defined as hypotension and was managed with intravenous fluids and incremental IV Mephentermine 6 mg. Injection Oxytocin 5mg bolus was given after delivery of the baby. Apgar scores were recorded at 1and 5 minutes. After surgery patient was shifted to post anaesthesia care unit and observed and blood pressure was noted every 15 min till patient was shifted to post operative ward after regression of sensory and motor block.

Intraoperative pain was evaluated using the Visual Analogue Scale (VAS), a scale from 0 to 10, whenever the patient experienced discomfort or pain during the procedure. When the VAS score exceeded 4, the patient was given injectable tramadol 50mg. Following the surgery, vital signs such as pulse and blood pressure were only checked at various time points- 1, 2, 4, 6, 10-, 20-, 40-, and 60-minutes post-surgery¹¹.

The research data was analyzed using a variety of statistical methods. The Kolmogorov-Smirnov test was utilized to assess the normality of continuous data, while categorical data was presented in terms of frequency and percentage. Descriptive statistics such as mean and standard deviation were used to

represent continuous data. The Statistical Package for the Social Sciences (SPSS-21) software by IBM in Chicago, USA was used for statistical analysis. Graphs illustrating the data were generated using Prizm software. A p-value less than 0.05 was considered statistically significant to determine the significance of the results.

RESULTS

The research involved 210 patients of ASA PS II who were scheduled for elective cesarean section. They were randomly

split into two groups (Group A: received Bupivacaine and Fentanyl and Group B: only Bupivacaine) each consisting of 105 LSCS patients. The average age of LSCS patients in group A was 25.3 ± 4.09 years, while the average age in group B was 24.6 ± 3.48 years. The p-value for the mean age comparison between the two groups was calculated as 0.174, indicating that it was not statistically significant. The study found that there was no notable variance among the groups based on ASA grading, as well as no significant discrepancies in parity, BMI, and gestational age as evidenced by a p-value greater than 0.05 in Table 1.

Table 1: Baseline characteristics of study groups

Parameters		Group A (N=105)	Group B (N=105)	P value
Age (years)		25.31±4.07	24.6±3.48	0.174
ASA (II)		95/10	97/8	0.623
BMI		35.47±6.05	34.26±5.81	0.141
Parity (n, %)	I	29 (27.6)	25 (23.8)	0.528
	>I	76 (72.4)	80 (76.2)	
Gestational Age (weeks)		38.3±0.87	38.5±0.93	0.109
Duration of operation (minute)		63.19±6.91	66.73±7.38	0.0004*

Group A exhibited a faster onset of sensory block compared to group B, with times of 1.3 ± 0.81 minutes and 1.7 ± 0.93 minutes, respectively ($p = 0.001$). Furthermore, T6 levels were achieved more quickly in group A than in group B in LSCS patients. The average time for complete sensory recovery was 140.7 ± 3.91 minutes for group A and 113.69 ± 2.22 minutes for group B,

showing statistical significance with a p-value of <0.001 ($p < 0.01$). The duration of effective analgesia was also significantly longer in group A, lasting 196.77 ± 6.13 minutes compared to 124.6 ± 5.08 minutes in group B, with a p-value of <0.001 ($p < 0.01$) (Table 2).

Table 2: Duration of sensory block statistics between two group

Variables	Group A (N=105)	Group B (N=105)	P value
Sensory block onset (min)	1.3±0.81	1.7±0.93	0.0011
Sensory block time to achieve peak sensory level (min)	3.27±1.62	5.52±2.17	<0.0001
Sensory block time for complete sensory recovery (min)	140.7±3.91	113.69±2.22	<0.0001
Sensory block duration of effective analgesia (min)	196.77±6.13	124.6±5.08	<0.0001

LSCS patients of Group A exhibited a faster onset of motor blockade, taking an average of 3.01 ± 0.64 minutes, compared to Group B which took 4.73 ± 0.85 minutes for the motor blockade to set in. This indicates that Group A experienced motor blockade 36.6% faster than Group B. All patients in both groups

experienced a total cessation of motor function. The average time for motor function to recover in group A was 176.9 ± 8.27 minutes, while in group B it was 140.18 ± 5.5 minutes, with a significant difference of $p < 0.001$ as depicted in Table 3.

Table 3: Comparison of motor blockage between two groups

Variables	Group A (N=105)	Group B (N=105)	P value
Onset of motor block (min)	3.01±0.64	4.73±0.85	<0.001
Time to reach maximum level (min)	8.43±1.05	10.1±1.39	<0.001
Total duration of motor block (min)	176.9±8.27	140.18±5.5	<0.001

There was significant difference between the two groups with respect to blood pressure, 9 patients in group A had hypotension and 28 patients in group B had hypotension. Group B experienced a higher incidence of hypotension at 26.6% compared to 8.6% in group A, (Figure 1). Other issues such as nausea, vomiting, and shivering were mild and did not necessitate further intervention. None of the patients experienced respiratory depression, and

the Apgar scores of the newborns at one minute and five minutes ranged between 7 and 10 across all groups. Nausea was reported in 10.4% of patients in group A and shivering in 12.6%, while in group B, nausea was reported in 7.6% of patients and shivering in 10.5%. Vomiting was reported in only 6-8% of patients in both groups, which was not deemed statistically significant ($p > 0.05$).

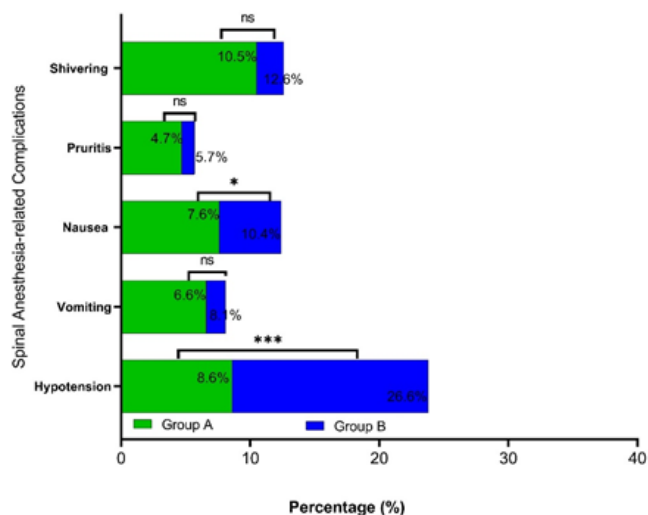


Fig 1: Graphical representation displaying the prevalent intraoperative issues experienced by distinct patient groups during elective cesarean deliveries. Ns: non-significant; *: $p < 0.05$; ***: $p < 0.001$.

DISCUSSION

Patients who are undergoing LSCS with spinal anesthesia may experience improved comfort during the procedure when a combination of local anesthetic and opioid agents is used. This can lead to a longer-lasting spinal analgesic effect and reduce the need for additional pain relief after the surgery¹²⁻¹⁴. However, it is important to consider potential side effects such as hypotension, itching, nausea, dizziness, and breathing difficulties. Fentanyl and bupivacaine are the most chosen drugs for spinal anesthesia during cesarean sections due to their availability in preservative-free forms and their ability to quickly penetrate nerve tissue, which helps prevent the spread of the anesthesia to the brain and spinal cord¹⁵.

The research involved 210 LSCS patients who were ASA PS II and were scheduled for elective cesarean section. Each patient was assigned randomly to one of two groups: Group A, which received a combination of Bupivacaine and Fentanyl, and Group B, which only received Bupivacaine. Both groups of patients had similar age, body mass index (BMI), number of previous pregnancies (parity), and stage of pregnancy (gestational age). Our research found that the time for sensory block development was significantly faster in group A compared to group B with times of 3.27 ± 1.62 minutes and 5.52 ± 2.17 minutes, respectively. This aligns with findings from other studies^{13, 15}. Interestingly, del-Rio-Vellosillo et al.¹⁶ and Leo did not observe any difference in sensory block development. Therefore, conflicting results exist regarding the speed of sensory block development.

In the group that received bupivacaine and fentanyl, there was a noticeable 36.6% incidence of complete motor block development, which was notably different from the group that only received bupivacaine. These findings are in line with previous research⁹. Interestingly, some authors have suggested that bupivacaine alone may be just as effective as the combination of

bupivacaine and fentanyl in producing a quality motor block¹⁷. On the other hand, literature stated that bupivacaine was found to be equally effective as the combination of bupivacaine and fentanyl in terms of motor block quality¹⁸. However, the duration of anesthesia was observed to be extended when bupivacaine was administered on its own⁷.

The study showed that both high and low-dose bupivacaine groups (Group B), with or without fentanyl, resulted in a significant decrease in blood pressure during the first 30 minutes of spinal anesthesia compared to the bupivacaine plus fentanyl group (Group A). The rate of hypotension in group A was recorded at 8.6%, while group B had a higher incidence at 26.6%. When fentanyl was added to bupivacaine, a significant decrease in the occurrence of hypotension was observed in LSCS patients. Adverse effects like nausea, headaches, and tremors were also noticed. The number of patients experiencing side effects was lower in the group receiving bupivacaine plus fentanyl (group A) compared to group B which received bupivacaine alone. However, the difference was not significant except for nausea. Nausea and vomiting after the administration of subarachnoid opioids happen due to their interaction with the opioid receptor of the chemoreceptor trigger zone at the base of the fourth ventricle^{8, 9}. Interestingly, the same low dose can enhance the block of local anesthetics, reducing nociceptive stimulation during procedures like peritoneal traction and uterine externalization. This can help decrease nausea and vomiting⁸. The discovery aligns with past research led by Sjoenen et al.¹⁹ which investigated the impact of various doses of bupivacaine on both hemodynamic stability and pain management. Additional studies by Venkata et al.²⁰, Sudan et al.²¹ and Piacherski and Muzyka,²² further corroborated our results, indicating that the addition of fentanyl to bupivacaine resulted in a notable reduction in hypotension occurrences. Overall, the combination of Intrathecal Fentanyl and Bupivacaine has proven to be more successful in decreasing hypotension during Lower Segment Cesarean Section (LSCS). The results of this research endorse the utilization of this combination in real-world medical applications.

CONCLUSION

Our study concludes that bupivacaine combined with intrathecal fentanyl is effective in reducing the incidence of hypotension during elective LSCS under subarachnoid block. Additional research is needed to determine this combination's optimal dosage and timing.

LIMITATIONS OF THE STUDY Patients with ASA physical status II were only involved in this study. So, these results might not be applicable in patients with higher grades. The sample size of the study was small and was carried out at only one institution which was too small for broad generalization.

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CONFLICT OF INTEREST None

FINANCIAL DISCLOSURE None

REFERENCES

- Duggappa DR, Lokesh MP, Dixit A, Paul R, Rao RR, Prabha P. Perfusion index as a predictor of hypotension following spinal anaesthesia in lower segment caesarean section. *Indian journal of anaesthesia*. 2017 Aug 1;61(8):649-54. DOI: [10.4103/ija.IJA_429_16](https://doi.org/10.4103/ija.IJA_429_16). PMID: 28890560
- Artawan IM, Sarim BY, Sagita S, Dedi MA. Comparison the effect of preloading and coloadng with crystalloid fluid on the incidence of hypotension after spinal anesthesia in cesarean section. *Bali Journal of Anesthesiology*. 2020 Jan 1;4(1):3-7. DOI: [10.4103/BJOA.BJOA_62_20](https://doi.org/10.4103/BJOA.BJOA_62_20)
- Uppal V, Retter S, Shanthanna H, Prabhakar C, McKeen DM. Hyperbaric versus isobaric bupivacaine for spinal anesthesia: systematic review and meta-analysis for adult patients undergoing noncesarean delivery surgery. *Anesthesia & Analgesia*. 2017 Nov 1;125(5):1627-37. DOI: [10.1213/ANE.0000000000002254](https://doi.org/10.1213/ANE.0000000000002254) PMID:28708665
- Wainger BJ, Macklin EA, Vucic S, McIllduff CE, Paganoni S, Maragakis NJ, Bedlack R, Goyal NA, Rutkove SB, Lange DJ, Rivner MH. Effect of ezogabine on cortical and spinal motor neuron excitability in amyotrophic lateral sclerosis: a randomized clinical trial. *JAMA neurology*. 2021 Feb 1;78(2):186-96. DOI: [10.1001/jamaneurol.2020.4300](https://doi.org/10.1001/jamaneurol.2020.4300).
- Satapathy S, Nayak LK, Behera SK, Satapathy GC, Swain R, Das S, Satapathy Jr S, Swain Jr R. A Comparative Study of Intrathecal Fentanyl and Nalbuphine as an Adjuvant to Hyperbaric Bupivacaine for Spinal Anesthesia in Lower Limb Orthopedic Surgeries: A Prospective, Double-Blind, Randomized Controlled Study. *Cureus*. 2023 Jun 30;15(6). DOI: [10.7759/cureus.41230](https://doi.org/10.7759/cureus.41230). PMID: 37529511
- Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. *Journal of anaesthesiology clinical pharmacology*. 2011 Jun 1;27(3):339-43. DOI: [10.4103/0970-9185.83678](https://doi.org/10.4103/0970-9185.83678). PMID: 21897504
- Abate SM, Belihu AE. Efficacy of low dose bupivacaine with intrathecal fentanyl for cesarean section on maternal hemodynamic: Systemic review and meta-analysis. *Saudi Journal of Anaesthesia*. 2019 Oct 1;13(4):340-51. DOI: [10.4103/sja.SJA_17_19](https://doi.org/10.4103/sja.SJA_17_19). PMID: 31572080
- Cowan CM, Kendall JB, Barclay PM, Wilkes RG. Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia. *British Journal of Anaesthesia*. 2002 Sep 1;89(3):452-8. PMID: 12402725
- Ebrie AM, Woldeyohanis M, Abafita BJ, Ali SA, Zemedkun A, Yimer Y, Ashebir Z, Mohammed S. Hemodynamic and analgesic effect of intrathecal fentanyl with bupivacaine in patients undergoing elective cesarean section; a prospective cohort study. *Plos one*. 2022 Jul 7;17(7):e0268318. DOI: [10.1371/journal.pone.0268318](https://doi.org/10.1371/journal.pone.0268318)
- Ousley R, Egan C, Dowling K, Cyna AM. Assessment of block height for satisfactory spinal anaesthesia for caesarean section. *Anaesthesia*. 2012 Dec;67(12):1356-63. DOI: [10.1111/anae.12034](https://doi.org/10.1111/anae.12034)
- Arzola C, Wiczorek PM. Efficacy of Low-dose Bupivacaine in Spinal Anesthesia for Cesarean Delivery: Systematic Review and Meta-analysis. *Obstetric Anesthesia Digest*. 2012 Sep 1;32(3):194-5. DOI: [10.1093/bja/aer200](https://doi.org/10.1093/bja/aer200)
- Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. *The Journal of the American Society of Anesthesiologists*. 1999 Dec 1;91(6):1919-. DOI: [10.1097/00000542-199912000-00045](https://doi.org/10.1097/00000542-199912000-00045)
- Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, Hertwig LM, Ostheimer GW. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. *Anesthesiology*. 1989 Oct 1;71(4):535-40. DOI: [10.1097/00000542-198910000-00009](https://doi.org/10.1097/00000542-198910000-00009)
- Graham D, Russell IF. A double-blind assessment of the analgesic sparing effect of intrathecal diamorphine (0.3 mg) with spinal anaesthesia for elective caesarean section. *International Journal of Obstetric Anesthesia*. 1997 Oct 1;6(4):224-30. DOI: [10.1016/s0959-289x\(97\)80027-1](https://doi.org/10.1016/s0959-289x(97)80027-1)
- Khosravi F, Sharifi M, Jarineshin H. Comparative study of fentanyl vs dexmedetomidine as adjuvants to intrathecal bupivacaine in cesarean section: a randomized, double-blind clinical trial. *Journal of Pain Research*. 2020 Oct 7:2475-82. DOI: [10.2147/JPR.S265161](https://doi.org/10.2147/JPR.S265161)
- del-Rio-Vellosillo M, Garcia-Medina JJ, Abengochea-Cotaina A, Pinazo-Duran MD, Barbera-Alacreu M. Spinal anesthesia for knee arthroscopy using isobaric bupivacaine and levobupivacaine: anesthetic and neuroophthalmological assessment. *BioMed research international*. 2014 Jan 1;2014. DOI: [10.1155/2014/349034](https://doi.org/10.1155/2014/349034)
- Burke D, Kennedy S, Bannister J. Spinal anesthesia with 0.5% S (-)-bupivacaine for elective lower limb surgery. *Regional Anesthesia and Pain Medicine*. 1999 Nov 1;24(6):519-23. DOI: [10.1016/S1098-7339\(99\)90042-1](https://doi.org/10.1016/S1098-7339(99)90042-1)
- Sia AT, Tan KH, Sng BL, Lim Y, Chan ES, Siddiqui FJ. Hyperbaric versus plain bupivacaine for spinal anesthesia for cesarean delivery. *Anesthesia & Analgesia*. 2015 Jan 1;120(1):132-40. DOI: [10.1213/ANE.0000000000000443](https://doi.org/10.1213/ANE.0000000000000443)

19. Sjoen GH, Falk RS, Hauge TH, Langesaeter E. Haemodynamic stability after paracervical block: A randomized, controlled, double-blind study comparing bupivacaine-adrenaline with bupivacaine. *Acta Anaesthesiologica Scandinavica*. 2019 Mar;63(3):373-80. DOI: [10.1111/aas.13259](https://doi.org/10.1111/aas.13259)
20. Venkata HG, Pasupuleti S, Pabba UG, Porika S, Talari G. A randomized controlled prospective study comparing a low dose bupivacaine and fentanyl mixture to a conventional dose of hyperbaric bupivacaine for cesarean section. *Saudi journal of anaesthesia*. 2015 Apr 1;9(2):122-7. DOI: [10.4103/1658-354X.152827](https://doi.org/10.4103/1658-354X.152827)
21. SudAn S, KAmAlAKShy RK, RAveendRAn S, SebAStiAn R. Incidence of Intraoperative Hypotension and Bradycardia in Spinal Anaesthesia with 0.5% Bupivacaine alone and 0.5% Bupivacaine with Fentanyl for Abdominal Hysterectomy: A Cross-sectional Study. *Journal of Clinical & Diagnostic Research*. 2022 Nov 1;16(11). DOI: [10.7860/JCDR/2022/59764.17009](https://doi.org/10.7860/JCDR/2022/59764.17009)
22. Piacherski V, Muzyka L. Comparison of the efficacy of 0.5% isobaric bupivacaine, 0.5% levobupivacaine, and 0.5% hyperbaric bupivacaine for spinal anesthesia in lower limb surgeries. *Scientific Reports*. 2023 Feb 15;13(1):2736. DOI: [10.1038/s41598-023-29711-9](https://doi.org/10.1038/s41598-023-29711-9)