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Original Article

Comparison of Intrathecal Bupivacaine Versus Bupivacaine plus Dexmedetomidine for Postoperative Pain Relief in Terms of Quality and Duration

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ABSTRACT

Objective: To measure the clinical efficacy of intrathecal Bupivacaine alone versus intrathecal Bupivacaine plus Dexmedetomidine on postoperative pain alleviation in terms of quality and duration in women undergoing C-section

Study Design: Randomized controlled trial, (Iranian Clinical Trial Registry: 76165)

Place and Duration of Study: Department of Anaesthesiology, PAF Hospital (Faisal), Karachi Pakistan from Sep, 2023 to Feb 2024.

Methodology: After registration with trial registry (ICTR) and ethical approval, this randomized controlled trial was performed in Anaesthesia department of PAF Hospital (Faisal), Karachi. Intrathecal Dexmedetomidine was given as an adjuvant to Bupivacaine in 33 gravid ladies (Group A) after randomization. Group A and Group B patients were followed for 24 hours post-operatively to assess duration and quality of analgesia. Statistical significance was compared between both study Groups.

Results: At twenty-four hours of time lapse, 2(6.1%) Group A patients had mild pain, 24(72.7%) had moderate pain and 7(21.2%) had severe pain compared to 7(21.2%) Group B patients who had moderate pain and 26(78.8%) had severe pain with *p*-value <0.001. The frequency of rescue analgesia was three times in 1(3.0) Group A and 10(30.3) Group B patients. The mean dose of analgesic ketorolac used by Group A patients was 53.64±23.4 milligrams with median dose of 60mg (IQR 30-120) compared to 110.91±19.099 milligrams in Group B with median dose of 120.0mg (IQR 60.0-150.0).

Conclusion: We concluded that intrathecal Dexmedetomidine provides better postoperative analgesia in terms of quality and duration when used as an adjuvant with local anesthetic Bupivacaine.

Keywords: Bupivacaine, Cesarean Section, Dexmedetomidine and spinal Anaesthesia.

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INTRODUCTION

Postoperative pain that is not well managed can dramatically increase the risk of complications for surgical patients. Early recovery is very crucial for a patient who is anticipated to care for her newborn soon after surgery.[1] Given that cesarean sections are among the most frequent operations performed on women of reproductive age, they require additional attention.[2] Enhanced recovery of mother improves neonatal outcomes. It helps to improve breastfeeding and mother-child bonding which is adversely affected by pain.[3] The ideal post-CS analgesic regimen should be effective while not interfering with the mother's ability to care for the newborn and with minimal drug transfer through breast milk.[4] Adjuvants are drugs that when delivered that when administered intrathecally concurrently, decrease the onset time and increase the duration and mitigate the adverse effects of local anesthetics.[5] Dexmedetomidine (DEX), a highly selective 2-adrenergic agonist with a receptor affinity greater than clonidine, exerts its effects via a variety of mechanisms.[6] Dexmedetomidine (Dex) has recently been studied for its potential to extend the duration of analgesia in peripheral and central nerve blocks.[7] No previous study of this kind has ever been conducted in our nearby populace hence we ought to assess the analgesic effect of intrathecal hyperbaric Bupivacaine alone versus intrathecal hyperbaric Bupivacaine plus Dexmedetomidine on postoperative pain relief.

Bupivacaine alone is the standard practice for subarachnoid block however addition of Dexmedetomidine to hyperbaric Bupivacaine is a recent practice. Paramasivan et al demonstrated that intrathecal Dexmedetomidine was associated with lower pain scores compared to placebo after 24 hours.[8] In our setup we use Bupivacaine only for regional Anaesthesia for cesarean section but the patients start making complain of pain in immediate post-operative period. W0065 want to use an adjuvant that can provide pain relief over extended period of time.

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Therefore the rationale of our RCT is to find the clinical significance of Dexmedetomidine for post-operative analgesia.

METHODOLOGY

After receiving approval from the Institutional Ethics Committee with FRPMC-IRB-2023-02 and registration with Iranian registry of clinical trial (Trial number: 76165), our randomized controlled trial was carried out at department of Anaesthesia at PAF Hospital (Faisal), Karachi Pakistan from September, 2023 to February 2024. The sample size was estimated using the WHO sample size calculator, by taking Level of significance =5% with power = 80%, the anticipated mean duration of analgesia with Dexmedetomidine (P1) to be 5509 minutes and anticipated mean duration of analgesia without Dexmedetomidine (P2) to be 2109 minutes .The estimated sample size came out 31. For drop our purpose: n/(1-d) where n=sample size calculated that is 31 and d= dropouts, ~5% so 31/(1-0.05)=32.6~33. The total sample size was 66 before randomization. Two Groups were created after randomization labelled as Group A comprising 33 patients who recieved intrathecal Dexmedetomidine (5ug) and Group B comprising 33 patients and only received intrathecal Bupivacaine.

Inclusion Criteria: Parturient undergoing elective caesarean section under spinal anaesthesia, American Society of Anaesthesiologists physical status classification (ASA) of II to III who signed written-informed consents.

Exclusion Criteria: Parturient who experienced failed spinal anaesthesia and required general anaesthesia, known cases of neurological and coagulation disorders, those with uncontrolled hypertension, Diabetes Mellitus, peptic ulcer, liver cirrhosis, contraindications to spinal anaesthesia, emergency caesarean section, patient allergic to Bupivacaine or Dexmedetomidine and those who were not able to understand the Numerical pain scale.

At study entry baseline demographics (age, weight on weighing machine, height, BMI, ASA score and co-morbidities, allergies) were recorded. Before caesarean section, each patient was thoroughly investigated which included a systemic examination, a thorough physical examination, and a detailed review of their medical history. Prior to surgery, routine investigations (such as coagulation profile, hepatitis profile, random blood sugar levels, and complete blood picture) will be evaluated. During the pre-anesthetic assessment every patient received a thorough explanation about participation in the study. The grading of pain perception was done on basis of Numerical pain score 10 using a horizontal line, 10 cm in length ranging from 0-10. On NRS pain scale , 0-1 meant no pain, 2-3 meant mild pain, 4-6 corresponded to moderate pain and 7-10 was taken as severe pain as shown in Table.[11] The participants were ensured that they had the option to leave the study at any time.

Randomization was performed by OT assistant who will not further help in the study. The patient allocation was hidden by means of sealed envelopes. Both the study participants and the researchers evaluating the results were kept blinded to the Group assignment. 33 patients received intrathecal 1.5 ml of 0.75% hyperbaric Bupivacaine (11.25mg) plus 5 µg Dexmedetomidine (Group A) while 33 patients received intrathecal 1.5ml of 0.75% hyperbaric Bupivacaine (11.25mg) Group B . Patients were attached standard monitoring and were preloaded with 12–15 mL/kg ml of ringer lactate. Sensory level was assessed by loss of sensation to spirit swab and surgery was allowed to proceed after confirming sensory block (level T4) and motor block (Bromage 1).[12] Pretreatment with 0.1mg/kg of Ondansetron was done. Hypotension (a decline in systolic blood pressure of more than 20% from the baseline or a reduction below 90 mmHg) was treated with additional intravenous fluid (4 mL/ kg) repeated 2 times and if this failed to reverse the hypotension then increments of intravenous (IV) phenylephrine were repeated. Bradycardia (heart rate <50 beats per min) was treated with 0.6 mg atropine. The side effects of the study drugs including hypotension, bradycardia, shivering and nausea-vomiting were noted. Following transfer to the postoperative recovery room postoperative pain scores and analgesia duration were documented together at 0, 2, 4 , 6, 12 and 24 hours. All patients received injection Paracetamol (Bofalgan), 1gm I/V, 8 hourly following the surgery. Toradol, a rescue analgesic, 30 mg intravenously, was administered to who complained of pain upon assessment at time intervals specified or other than that. The time of the first rescue analgesic (FRA) request was recorded. The total consumption of rescue analgesic for the first 24 hours after surgery was also noted. Primary outcomes were the quality of pain relief that measured using numerical pain scale, the number of times (frequency) rescue analgesia requested and total dose of rescue analgesia given in 24 hours period post-operatively . Secondary outcomes were the duration of analgesia assessed by

the time to first rescue analgesia (FRA) and side effects. The study flow diagram is mentioned in Figure. Total 66 patients were randomized and none of the patient was dropped from the study and all patients completed study protocol.

Data was recorded on statistical package of social science (SPSS) version 26. The frequency & percentage of adverse effects were recorded along with other qualitative variables. The Mean±SD was computed for quantitative variables. The comparison was made with cross tabulation and chi-square analysis was employed. For quantitative variables like age, BMI and gestation mean was calculated along with standard deviation and independent sample t-test was applied. For non-normal variables, median and IQR was calculated and compared through Mann Whitney U test.

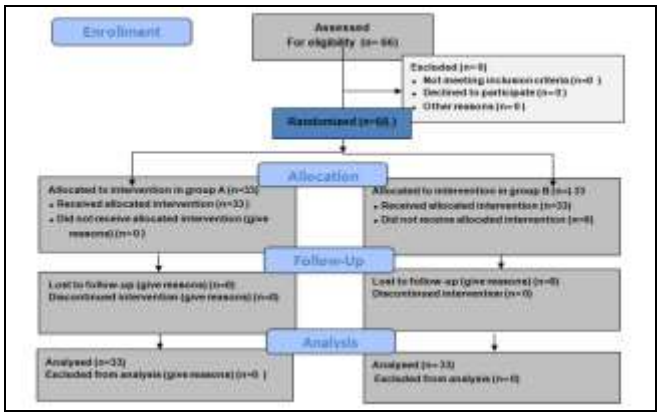

Figure: Phases of Randomized Controlled Trial (Consort Diagram)

RESULTS

Primary outcomes were the quality of pain relief that was measured using numerical pain scale as mentioned in methodology and the number of times (frequency) rescue analgesia was requested and median dose of rescue analgesia given in 24 hours period post-operatively . Secondary outcomes were the duration of analgesia assessed by the time to first rescue analgesia (FRA) and side effects. The demographic variables were fairly analogous and fortunately no patient was dropped out of the study. When we compared demographics the mean age of Group A patients was 28.39±5.45 years versus 27.18±5.32 years in Group B. Mean body mass index was 29.03±2.48 Kg/m^2 in Group A versus 28.61±2.58 Kg/m2 in Group B. The mean gestational age was 38.12±1.34 weeks in Group A versus 37.94±0.88 weeks in Group B. The parity had similar distribution among both Groups as presented in Table-II.

Table-I: Grading of Pain Perception on basis of Numerical Rating Scale (NRS)

Pain perception	Numerical Rating Scale
Absence of pain	0-1
Mild pain	2-3
Moderate pain	4-6
Severe pain	7-10

Table-II: The Demographics of Pregnant ladies included in Study Groups (n=66)

		Group A n=33 Mean±SD	Group B n=33 Mean±SD	*p*-value
Age (years)		28.39±5.45	27.18±5.32	0.262
Body Mass Index (Kg/m^2)		29.03±2.48	28.61±2.58	0.896
Gestational Age (weeks)		38.12±1.34	37.94±0.88	0.033
		Frequency(%)	Frequency(%)	
Parity	Primigravida	2(6.1)	1(3.0)	0.388
	Previous one LSCS	14(42.4)	8(24.2)	
	Previous two LSCS	11(33.3)	13(39.4)	
	Previous three LSCS	4(12.1)	9(27.3)	
	Previous four LSCS	2(6.1)	2(6.1)	

**LSCS: Lower Segment Caesarean Section*

The patients in Group A had better pain scores compared to Group B as shown in Table-III. 33(100%) patients in Group A experienced no pain immediately after surgery (zero hours) while only 2(6.1%) experienced pain in Group B at zero hours with *p*-value of 0.246. After three hours of surgery, 23(69.7%) of Group A patients experienced no pain as per operational definition, 8(24.2%) had mild pain, 2(6.1%) had moderate pain and none of them had severe pain while 24(72.7%) of Group B patients had moderate pain and 9(27.3%) had severe pain with *p*-value <0.001. Six hours post-operatively, 27(81.8%) Group A patients only had mild pain, 5(15.2%) had moderate pain and only one experienced severe pain. Eighteen (54.5%) Group B patients had moderate pain when they requested rescue analgesia and 15(55.5%) had severe pain. After 12 hours of surgery, 11(33.3%) Group A patients had mild pain and none of the Group B patients had mild pain rather 23(69.7%) Group B patients had severe pain necessitating rescue analgesia. At twenty-four hours of time lapse, 2(6.1%) Group A patients had mild pain, 24(72.7%) had moderate pain and 7(21.2%) had severe pain compared to 7(21.2%) Group B patients who had moderate pain and 26(78.8%) had severe pain with *p*-value <0.001. 10(30.3%) Group B patients made three rescue analgesic requests compared to 1(3.0%) Group A patients. 13(39.4%) Group A patients requested rescue analgesia only once and only 2(6.1%) patients made four requests contrary to 20(60.6%) patients in

Group B who made four requests. 2(6.1%) patients in Group B even made five analgesic requests in 24 hours period. The mean dose of analgesic ketorolac used by Group A patients was 53.64±23.4 milligrams with median dose of 60mg (IQR 30-120) compared to 110.91±19.099 milligrams in Group B with median dose of 120mg (IQR 60-150).

Table-III: Primary and Secondary Outcomes : Frequency of Different Pain Scores, Rescue Analgesia and Mean Frequency Rescue Analgesia (n=66)

		Group A n=33 n (%)	Group B n=33 n (%)	*p*-value
Pain perception at zero hours	No pain	33(100)	31(93.9)	0.246
	Mild pain	0(0)	2(6.1)	
Pain perception at 3 hours	No pain	23(69.7)	0(0)	<0.01
	Mild pain	8(24.2)	0(0)	
	Moderate pain	2(6.1)	24(72.7)	
Pain perception at 6 hours	Severe pain	0(0)	9(27.3)	<0.01
	Mild pain	27(81.8)	0(0)	
	Moderate pain	5(15.2)	18(54.5)	
Pain perception at 12 hours	Severe pain	1(3.0)	15(55.5)	<0.01
	Moderate pain	19(57.5)	10(30.3)	
	Severe pain	3(9.1)	23(69.7)	
Numerical rating score (NRS) at 24 hours	Mild pain	2(6.1)	0(0)	<0.01
	Moderate pain	24(72.7)	7(21.2)	
	Severe pain	7(21.2)	26(78.8)	
Frequency Rescue Analgesia	1	13(39.4)	0(0)	<0.01
	2	17(51.5)	1(3.0)	
	3	1(3.0)	10(30.3)	
	4	2(6.1)	20(60.6)	
	5	0(0)	2(6.1)	
Median Rescue Analgesic (Ketorolac) consumed in 24 hours (milligram)		60.0 (IQR 30.0-120.0)	120 (60.0-150.0)	<0.001

The frequency of side effects (Table-VI) did not show significant difference between the study Groups except for shivering. 1(3.0%) Group A patient complained of shivering while 13(39.4%) Group B patients developed shivering which shows that intrathecal Dexmedetomidine has anti-shivering effect.

Table-IV: Comparison of Side Effects (n=66)

Side Effects		Group A n=33 Frequency (%)	Group B n=33 Frequency (%)	*p*-value
Nausea & vomiting	Yes	4(12.1)	7(21.2)	0.285
	No	29(87.9)	25(75.8)	
Shivering	Yes	1(3.0)	13(39.4)	<0.001
	No	32(97.0)	20(60.6)	
Hypotension	Yes	4(12.1)	5(15.2)	0.500
	No	29(87.9)	28(84.8)	
Bradycardia	Yes	2(6.1)	3(9.1)	0.500
	No	31(93.9)	30(90.9)	

DISCUSSION

The incidence of C-section has increased tremendously over the past few years with postoperative pain being among the most common undesirable clinical outcomes linked to a cesarean (C-section). Early recovery is significant for an obstetric patient having surgical recovery requirements, such as breastfeeding, and caring for her newborn soon after surgery, which might be hampered by inadequate postoperative analgesia hence this study is targeted on women undergoing C-section to reduce. When Dexmedetomidine is combined with Bupivacaine in spinal Anaesthesia in women undergoing elective C-section it improves post-operative analgesia as demonstrated by our trial. Not only the pain scores reduced indicating improved quality of analgesia but also the frequency of analgesic requests diminished with Dexmedetomidine. Liu *et al*.[13] demonstrated that the intrathecal Dexmedetomidine was comparable to intravenous Dexmedetomidine in prolonging the post-operative analgesia. It also accelerated the onset of sensory blockade. In our patients we used intrathecal route as intravenous route was not good option in pregnant females who need to feed their neonates in post-operative period. James *et al*.[14] studied Dexmedetomidine with intrathecal morphine in knee arthoplasty patients. They didn't not find any additional improvement in quality of analgesia. However we demonstrated a substantial improvement in quality and duration of analgesia. The difference of demographics was a major difference in our and their study. The greater response to local anesthetic effect of Dexmedetomidine can partly be explained by reduced median effective concentration to produce analgesia (MLAC).[15] The reduction of MLAC by Dexmedetomidine has been studied by Ye *et al*.[16] by retrobulbar use Dexmedetomidine as an adjuvant to bupicaine for retinal surgery. However, more studies are required to confirm its effect on MLAC.

According to RCT conducted by Mowar *et al*.[17] there was significant prolongation of FRA due to Dexmedetomidine with mean FRA to be 738 minutes which is comparable to our study with mean FRA of 840 minutes (14 hours). However they used 10ug and we used 5ug of Dexmedetomidine. However they excluded the gravid ladies. Pregnancy causes engorgement of epidural venous plexus and the dose of local anesthetic is reduced by 30 percent. This parly explains the similarity of FRA between Nanji *et al*.[18] and our study despite using different doses of Dexmedetomidine . Shivering is an un-desirable effect of labor and spinal anesthesia whose frequency was low in patients with Dexmedetomidine in our patients. This role of Dexmedetomidine has been

highlighted by Nasseri K, *et al*., in their study.[19] This multi-dynamicity of Dexmedetomidine make makes it a favorable adjuvant.

CONCLUSION

We concluded that intrathecal Dexmedetomidine provides better postoperative analgesia in terms of quality and duration when used as an adjuvant with local anesthetic Bupivacaine.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

ZA & ZAR: Data acquisition, critical review, approval of the final version to be published.

SS & MK: Conception, study design, drafting the manuscript, approval of the final version to be published.

MS & NUS: Data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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