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Effect of Local Wound Infiltration with Ketamine versus Dexmedetomidine on Post-operative Pain Relief in Terms of Quality and Duration after Cesarean Section

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ABSTRACT

Objective: To measure the frequency of pain and duration of analgesia with two different adjuvants (ketamine & dexmedetomidine) with local anesthetic bupivacaine for local wound infiltration after cesarean section for post-operative analgesia.

Study Design: Randomized Controlled Trial (IRCT: 74668).

Place and Duration of Study: Anesthesia department, Pakistan Air Force Hospital, Karachi Pakistan, from Jul to Dec 2023.

Methodology: The study was commenced after permission from the ethical committee with ERC number FRPMC-IRB-2023-03 & trial registration number#74668 9 (IRCT). It was a single center study and a sample of 142 was randomized into two groups: Groups A and B. In group A ketamine was employed as an adjuvant and in group B dexmedetomidine was used as an adjuvant. Quality of analgesia and duration of block was measured post-operatively in both groups to compare the drug under study.

Results: Twenty-seven (39.7%) of group B patients had mild pain and 41(60.3%) experienced moderate pain at 12 hours. Thirty-nine (54.9%) group A patients developed moderate pain while 32(45.1%) experienced severe pain necessitating rescue analgesia after twelve hours of surgery. The mean time to first rescue analgesia was also prolonged on group B patients with mean duration of analgesia in group B to be 15.49±3.2 hours versus 8.4±4.1 hours in group A with *p*-value of <0.001.

Conclusion: We concluded that dexmedetomidine was favorable adjuvant in terms of quality and duration of analgesia for local wound infiltration compared to ketamine.

Keywords: Dexmedetomidine, Ketamine, Lower Segment Cesarean Section (LSCS).

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INTRODUCTION

Lower segment cesarean section (LSCS) is a very frequent surgery and it is linked with considerably high pain intensity with pain scores soaring as high as nine to ten on pain scale.[1] The patients who are given epidural with a view to provide labor analgesia often get benefitted from the analgesic usefulness of epidural catheter as they get post-operative analgesics through this epidural catheter.[2] But the patients who are bound to undergo cesarean receive spinal anesthesia. The effect of spinal anesthesia wears off after almost ninety minutes.[3] When duration of cesarean stretches beyond usual time frame of 30 minutes to one hour patients start experiencing high intensity pain especially when bupivacaine is used alone without any adjuvant.[4] Under these circumstances its gets imperative to give additional analgesia to these patients in anticipation to prevent severe pain and discontent.

Local infiltration of wound is a main stay practice in resource limited setups where image guided blocks are not possible due to limited availability of ultrasound machine.[5] The lignocaine and bupivacaine are two local anesthetics which are in use for almost five decades but the use of adjuvants to enhance their efficacy is under constant progression. There are many adjuvants that have been used to improve the efficiency of these drugs like opioids, magnesium, tramadol, epinephrine, clonidine and dexamethasone.[6] All these adjuvants have their advantages and short comings.[7] There is conflicting evidence regarding use of ketamine. It is unpopular among some authors due to its psychomimetic effects when used as adjuvant to local anesthetics.[8] At the same time it has been shown to be of comparable efficacy to dexmedetomidine in terms of analgesia and even better to it in reducing stress response when given as adjuvant for wound infiltration.[9] Dexmedetomidine has been advocated for its use as adjuvant in peripheral nerve block and

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neuroaxial anesthesia but it is suggested to be off label for local wound infiltration by some authors.[10]

Both dexmedetomidine and ketamine are widely used in our setting and we want to employ them as adjuvant for local wound infiltration but there is conflicting evidence regarding their use. We want to study two aspects of ketamine and dexmedetomidine as an adjuvant to local anesthetics that is quality and duration of analgesia. The adjuvant that offers advantage in both aspects will be considered better.

METHODOLOGY

After seeking approval from ethical board (IERB Number: FRPMC-IRB-2023-03), and registration with IRCT with trial number: 74668, we performed this Randomized Controlled Trial at Department of Anesthesia, PAF Hospital (Faisal), Karachi (FRPMC) Hospitals Pakistan, from July to December 2023. The sample size was calculated with the help of WHO sample size calculator by taking confidence interval 95%, margin of error 5%, prevalence of postoperative analgesia after local infiltration of ketamine to be 24[11] and after dexmedetomidine to be 8.[11] The estimated sample size came out to be 64. We collected a sample of 142 patients through non-probability consecutive sampling and randomized them into two groups (71+71).

Inclusion Criteria: Women undergoing elective cesarean section under spinal anesthesia of ASA II class who have signed the written and informed consent will be included in this study after collaborating with the primary physician.

Exclusion Criteria: Parturients who refused or experienced failed spinal anesthesia and required general anesthesia, those who had an allergy to bupivacaine, ketamine, and dexmedetomidine, those who had neurological diseases, emergency surgery, contraindication to spinal, who were unable to understand the Numerical Pain Scale or those who had failed spinal anesthesia were excluded from the study.

Written informed consent was taken from all participants on a predesigned questionnaire. On the day of surgery, randomization was performed by the anaesthesia assistant who was not involved in the study. Before caesarean section, each patient was subjected to a complete preoperative assessment. All patients will be pretreated with 0.1mg/kg of ondansetron to prevent nausea and vomiting. Under strict aseptic measures, a subarachnoid block was administered to all patients while being seated on operating table. After administering bupivacaine (0.5%, 2.5ml) intrathecally the patients were immediately placed in the supine position with 30 degree leftward table tilt. Sensory level was assessed by loss of sensation to spirit swab and surgery was allowed to proceed after achieving sensory block up to level T4 and bromage 1 one on modified Bromage scale.[12] Patients received subcutaneous skin infiltration of the study drug as an adjunct to bupivacaine by the anesthetist at the end of the surgery after skin closure. Group A patients received ketamine as an adjuvant to local anesthetic bupivacaine. 40ml of 0.25% bupivacine with 2mg per kilogram of ketamine was infiltrated in the wound with help of 25 gauge needle at the end of surgery. In group B patients, 40ml of 0.25% bupivacine with 2microgram per kilogram body weight of dexmedetomidine was infiltrated in the wound with help of 25 gauge needle at the conclusion of surgery.

The primary outcome was the quality of analgesia gauged with Numerical Rating Score (NRS) measured at 0, 3, 6, 8, 12 and 24 hours. The secondary outcome was time to first rescue analgesia, the total frequency of analgesic requests in 24 hours and the frequency of side effects including bradycardia, hypotension and presence or absence of hallucinations in both study groups within eight hours post-anesthesia period. The demographic details including age, BMI, parity and gestational age were also noted down. The time at which the drug administration is completed will be recorded, and all durations will be calculated considering the time of drug administration as time zero. Hypotension was defined as a decrease in systolic blood pressure of more than 20% from the baseline or a decrease below 90 mmHg and it was treated intravenous (IV) phenylephrine. And symptomatic bradycardia was defined as heart rate <50 beats per min and was treated with 0.6 mg atropine. Following transfer to the postoperative recovery room severity of pain was measured by NRS13 (numerical pain rating scale). Patients were asked to rate their pain from a scale of 11 points 1cm apart with zero = no pain, 1-2 mild pain, 3-6 moderate pain and 7to 10 = severe pain as gauged by the NR scale. As part of a multimodal postoperative analgesic regimen, all patients were given injection paracetamol intravenous (one gram), 8 hourly following the surgery. Intravenous ketorolac (30mg) was rescue analgesic. Post-operatively, the total frequency of rescue analgesia required in each group over 24 hours

and the time of first rescue analgesic request was noted. Patient satisfaction was noted at 24 hours.

The data was processed with help of social package of statistical science (SPSS) Version 23. Means were calculated for quantitative variables and frequencies were calculated for qualitative variables. Chi-square analysis was applied to figure out statistical significance inform of *p*-value which was considered suggestive if found less than 0.05. The phases of randomized controlled trials are mentioned in Figure-1.

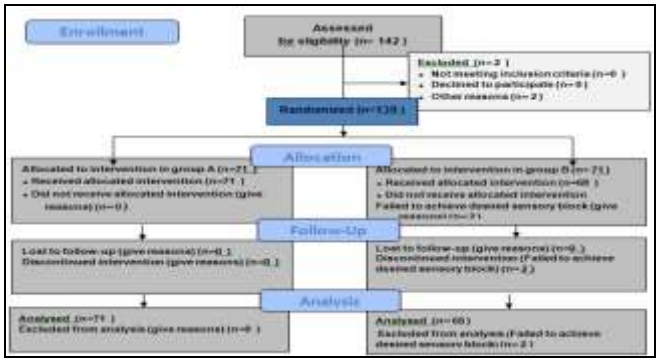

Figure-1: Phases of the Randomized Controlled Trial (Consort Flow Diagram 2010)

RESULTS

All the patients enrolled in group A successfully completed the research roadmap and none of the patients was dropped but two patients could not achieve level T4 in group B, therefore they were dropped out from results. The demographics were similar in both study groups. The mean age of group A patients was 26.10±5.59 years while mean age of group B patients was 28.40±2.5 years. The demographics are illustrated in Table-I.

Table-I: Demographics of Study Groups A (Ketamine) and B (Dexmedetomidine) (n=139)

		Group-A n=71 Mean±SD	Group-B n=68 Mean±SD	*p*-value
Age (Years)		26.10±5.59	25.71±3.16	0.14
BMI(Kg/m2)		27.69±2.38	27.07±2.04	0.07
Gestational age (weeks)		38.08±0.69	38.29±1.16	0.42
Duration of surgery (minutes)		57.75±16.94	63.87±19.17	0.08
		n(%)	**n(%)**	
Parity	Primigravida	15(21.1)	9(13.2)	0.44
	Previous One Cesarean Section	28(39.4)	32(47.1)	
	Previous Two Cesarean Sections	28(39.4)	27(39.7)	

Table-II: Quality and Duration of Analgesia in both Study Groups (n=139)

		Group A n=71 Frequency (%)	Group B n=68 Frequency (%)	*p*-value
Pain at 0 hours post-operatively	No pain	50(70.4)	40(58.8)	0.105
	Mild	21(29.6)	28(41.2)	
	moderate	0(0)	0(0)	
	severe	0(0)	0(0)	
Pain at 3 hours post-operatively	No pain	0(0)	0(0)	-
	Mild	71(100)	69(100)	
	moderate	0(0)	0(0)	
	severe	0(0)	0(0)	
Pain at 6 hours post-operatively	No pain	0(0)	0(0)	<0.001
	Mild	34(47.9)	49(72.1)	
	moderate	30(42.30	19(27.9)	
	severe	7(9.9)	0(0)	
Pain at 12 hours post-operatively	No pain	0(0)	0(0)	<0.001
	Mild	0(0)	27(39.7)	
	moderate	39(54.9)	41(60.3)	
	severe	32(45.1)	0(0)	
Pain at 24 hours post-operatively	No pain	0(0)	0(0)	<0.001
	Mild	0(0)	27(39.7)	
	moderate	25(35.2)	41(60.3)	
	severe	46(64.8)	0(0)	
Frequency of rescue analgesia	1	3(4.2)	48(70.6)	<0.001
	2	30(42.3)	3(4.4)	
	3	35(49.3)	5(7.4)	
	4	3(4.2)	12(17.6)	
		Mean±SD	**Mean±SD**	
Time to first rescue analgesia (hours)		8.4±4.1	15.49±3.2	<0.001

The primary outcome was the quality of analgesia quantified through Numerical Rating Score (NRS). At zero post-operative hours, 50(70.4%) group A patients and 40(58.8%) group B patients did not experience any pain. 21(29.6%) patients in group A experienced mild pain and 28(41.2%) patients experienced mild pain in group B. Only mild pain was experienced by both group A and B patients in immediate post-operative period up to 3 hours and there was no significant difference. 34(47.9%) group A patients experienced mild pain, 30(42.3%) experienced moderate pain and only 7(9.9%) patients experienced severe pain compared to group B patients after 6 hours of surgery. 27(39.7%) of group B patients had mild pain and 41(60.3%) experienced moderate pain at 12 hours and none of the patients had severe pain with *p*-value of <0.05. After twelve hours of surgery 39(54.9%) group A patients developed moderate pain while 32(45.1%) experienced severe pain necessitating rescue analgesia. At the same time 27(39.7%) group B patients had mild pain and 41(60.3%) experienced moderate pain while none of the group B patients

severe pain after twelve hours post-operatively with *p*-value <0.001 which shows that group B patients had better quality of analgesia. 46(64.8%) group A patients had severe pain in group A and no group B patients developed severe pain. The mean time to first rescue analgesia was also prolonged on group B patients with mean duration of analgesia in group B to be 15.49±3.28 hours versus 8.4±4.12 hours in group A with *p*-value of <0.001 as shown in Table-II.

Both drugs had comparable safety profile as there were minimum side effects in both study groups. The comparison of frequency of side effects has been made in Table-III. At the time of discharge patients were asked to register their experience whether they were satisfied with the drugs under study for providing adequate analgesia. Group B patients were more satisfied than group A patients as shown in Figure-2.

Table-III: Side Effects in both Study Groups Caused by both Drugs (n=139)

Side effect	Group A N=71 Frequency n(%)	Group B N=68 Frequency n(%)	*p*-value
Bradycadia	0(0)	0(0)	0.05
Hypotension	0(0)	1(5)	
Hallucinations	0(0)	0(0)	

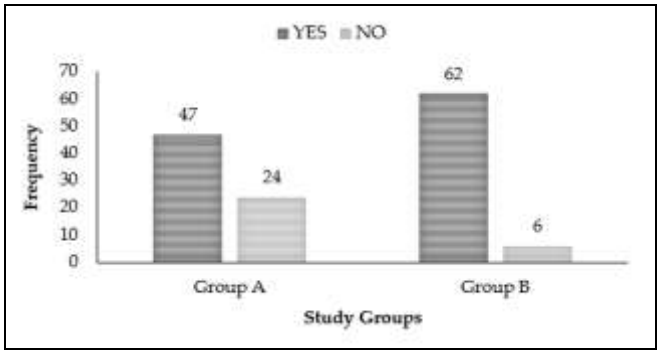

Figure-2: Patient Satisfaction in both Groups: Group A (n=71) and Group B (n=68)

DISCUSSION

Wound infiltration with local anesthetics is an old but efficacious, cost effective and quick option for delivering adequate postoperative analgesia with minimal associated adverse effects. It does not require much of operator's dexterity as it is very easy to be given and it is time effective as well. Incorporating ketamine or dexmedetomidine into a mixture of racemic bupivacaine mixture for local wound infiltration prolongs the time until the initial request for rescue analgesia and provides good quality anesthesia however dexmedetomidine is better than ketamine in both the quality and duration of analgesia.

Mohamed *et al.*,[14] analyzed the effects of ketamine and dexmedetomidine on post-operative pain after infiltrating them as local anesthetic adjuvant. Their study was a double-blind randomized trial and surgery was hysterectomy which was done under general anesthesia. They demonstrated that both drugs had opioid sparing effect but ketamine was more effective than dexmedetomidine. With ketamine the morphine requirement was around 6mg and with dexmedetomidine it was it was approximately 14 mg. The results of their trial were conflicting to our study as in our study pain scores were lower in dexmedetomidine group versus ketamine group.

Biomy *et al.*,[15] performed a research similar to ours as the surgery was same as cesarean section and both drugs under study were also same. They also favored ketamine. The patients in their study were given general anesthesia for cesarean section and their primary outcome was total dose of opioid pethidine used in 24 hours time period.

According to a systematic review of 89 randomized controlled trials and 126 original articles by British medical journal authored by Bai *et al.*, it was found that alpha-2 agonists were most reliable as adjuncts to local anesthesia among array of different additives like magnesium, ketamine and non-steroidal anti-inflammatory agents.[16]

Jiang *et al.*, used dexmedetomidine for local wound infiltration in patients undergoing total knee arthoplasy. Their study was a metaanalysis which analyzed 7 trails in which dexmedetomidine was used as adjunct to local anesthetic. The observed that mean duration of analgesia provided was four hours and up to a period of 12 hours. They suggested that dexmedetomidine ability to enhance analgesic duration of local anesthetic was more pronounced in abdominal surgeries. Although it has direct local anesthetic properties but it also limits the uptake of bupivacaine and delays hyperpolarization of cells.[17]

Azemati *et al.*, presented their experience after using dexmedetomidine as adjuvant to local anesthetic ropivacaine in pediatric patients. They demonstrated that there was substantial reduction in pain scores especially during first hour post=operatively. They also observed that dexmedetomidine caused sedation in pediatric patients without considerable hemodynamic changes. However our study included adult patients and sedation was not documented in any of them.[18]

Qiu *et al.*,[19] performed a metanalysis comparing analgesia by ketamine and dexmedetomidine in

pediatric patients undergoing dental treatment. They studied four trials including almost hundred and sixty patients of pediatric age group. However the findings of their metananlysis were inconclusive. They concluded that analgesia and sedation was similar with both adjuvants but they quality of evidence was low quality.

Hefni *et al*., used ketamine and dexmedetomidine for Pecs–II block for patients undergoing mastectomy. They used 1mg/kg ketamine versus 1ug/kg of dexmedetomidine as an adjunct to local anesthetic bupivacaine. They concluded that addition of dexmedetomidine to a mixture of bupivacaine was more effective than ketamine in causing analgesia which is similar to our findings.[20]

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LIMITATIONS OF STUDY

The study was single centre. The objective measurement of pain was not done.

CONCLUSION

We concluded that dexmedetomidine was favorable adjuvant in terms of quality and duration of analgesia for local wound infiltration compared to ketamine.

Conflict of Interest: None.

Funding Source: The hospitals resources were used.

Authors' Contribution

ZA & ZAR: Drafting of work, design analysis, data acquisition, data interpretation and approval of final version to be published

SS & MK: Data analysis, data acquisition, drafting of work, critical revision, approval of final version to be published

MS & AM: Drafting of work, critical review, approval of final version to be published.

All authors have consented to be held responsible for all aspects relating to authenticity and reliability of research work.

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