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Main subject [Obstetrics; Anesthesiology]\*



Original Article

## Ketamine versus Dexmedetomidine in Local Wound Infiltration for Postoperative Pain Relief in Cesarean Section

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### ABSTRACT

**Background:** Cesarean delivery is a frequently obstetric operation in Egypt with a recently reported over all cesarean section rate of 54% and it causes moderate to severe postoperative discomfort. Infiltration of the wound site is a method to improve postoperative analgesia.

**The aim of the work:** To compare the pain relief effects of ketamine versus dexmedetomidine combined to bupivacaine in local wound infiltration in patients undergoing cesarean section and to estimate side effects of medications.

**Patients and Methods:** This randomized, controlled study including 90 women were subjected for elective cesarean delivery under general anesthesia and were divided at random into 3 equal groups to receive 40 ml bupivacaine [0.25%] + either 2 mg/kg ketamine in [group A], 2 µg/kg dexmedetomidine in [group B] or 2 ml saline in [group C] via local wound infiltration. The primary outcome was the time of the first analgesia requested. The secondary outcomes were total dose of analgesia per 24 hours, visual analogue scale, the time of starting movement, breast-feeding, passing flatus or stool, start of eating and adverse effects of medications.

**Results:** A significant increase in time of the first analgesic request in group A [8.4 ±1.91] h. and group B [7.5±1.81] h. than group C [4.3±1.24] h. A significant decrease in pethidine consumption in group A [59 ± 28.93 mg] than group B [72 ± 23.1 mg] and group C [102 ±16 mg]. The visual analogue scale [VAS] was significantly lower [p<0.001] in groups A and B than in group C. The time of start movement, breast-feeding, passing flatus and eating was decreased in groups A and B than in group C.

**Conclusions:** Addition of ketamine or dexmedetomidine to local anesthetics wound infiltration increased time to the first analgesia request and decreased total analgesic consumption, but ketamine is superior.

**Keywords:** Ketamine; Dexmedetomidine; Local anesthesia; Wound Infiltration.

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\* Main subject and any subcategories have been classified according to the research topic.

## INTRODUCTION

post-cesarean pain is unpleasant sensation that occurs as a result of tissue damage, and indicates that the body has been injured [1].

Post-operative pain management is essential since women are expected to recover rapidly and care for their newborns within a few hours following surgery [2]. As a result, utilizing a safe, uncomplicated, and effective analgesic is recommended [3].

Effective postoperative analgesia can enhance recovery and decrease morbidity [4]. Local anesthetics wound infiltration is an adequate technique for pain management after many operations and can decrease postoperative analgesic requirements [5].

It is an easy, effective and costless technique can enhance postoperative analgesia for different types of operations without major complications [6].

In terms of somatic pain control, a variety of systemic and local anesthetic approaches have been employed to treat Post-cesarean pain [7].

Ketamine is a central and peripheral analgesic that works by blocking the N-methyl-D-aspartate [NMDA] receptor [8].

Dexmedetomidine is a highly selective agonist of  $\alpha$  2-adrenergic receptor with sedative, analgesic but not anesthetic characters. So, it's safe as an adjuvant in various clinical applications [8].

## AIM OF THE WORK

In the current work, we aimed to compare the pain relief effects of ketamine versus dexmedetomidine combined to bupivacaine in local wound infiltration in patients underwent cesarean section and to estimate side effects of medications.

## PATIENTS AND METHODS

Following the approval of the local ethics committee and the signed informed consent of each parturient, this randomized double-blind controlled study was conducted on 90 women American Society of Anesthesiologists [ASA] I and II. They were subjected to elective cesarean delivery under general anesthesia in Al-zahraa University Hospital from January 2019 to January 2020.

**Inclusion criteria** for pregnant women were, primigravida with singleton fetus, age between 20 and 40 years, weight between 60 and 85 kg and height between 155 and 170 cm, patients with no obstetric complication [pre-eclampsia and antepartum hemorrhage].

**Exclusion criteria** were patient refusal, multiple pregnancy, the procedure lasted more than one hour, drug abuse, history of allergy to the study drugs, diabetes mellitus, heart, liver, kidney, coagulation or mental disorders and local infection of previous cesarean scar.

Pre-operative assessment was done for each parturient before cesarean section by history [personal, medical, surgical, obstetric], examination [general, local and airway] and routine investigations. Each parturient was trained on the use of visual analogue scale [VAS] by an anesthesiologist who was not involved in the study. Visual analogue scale, which was used for pain assessment is a horizontal line, 10 cm in length ranging from 0 = [no pain] to 10= [worst pain].

A computer-generated random number was used to allocate the patients into one of the three groups: Group A [n=30]: given 40 mL of bupivacaine [0.25%] + 2 mg/kg ketamine by local wound infiltration. Group B [n=30]: given 40 mL bupivacaine [0.25%] +2  $\mu$ g/kg dexmedetomidine by local wound infiltration. Group C [n= 30]: given 40 mL bupivacaine [0.25%] + 2 ml saline by local wound infiltration.

Drugs used in wound infiltration were prepared by anesthesia residents who had no rule in the study.

In the operating room, intravenous cannula was inserted and ringer acetate solution [10 ml/kg/h] was started, patients were attached to the standard monitor [Fabius Gs, Germany] as electrocardiography, pulse oximetry and non-invasive blood pressure. Prior to the induction of anesthesia, the mother's heart rate [HR] and mean arterial pressure [MAP] were monitored.

After preoxygenation [for five minutes], women received general anesthesia by intravenous propofol [1.5 mg/kg], atracurium [0.5 mg/kg]. The maintenance of anesthesia was achieved by oxygen/ air mixture, sevoflurane [2%], atracurium [0.1 mg/kg] if required and fentanyl 50  $\mu$ g, after delivery of the fetus, HR and MAP were recorded each 10 minutes interval through the surgery.

Before wound closure, women received intra-incisional infiltration of 40 ml bupivacaine [0.25%] plus either 2 mg/kg ketamine in [group A], 2  $\mu$ g /kg dexmedetomidine in [group



B] or 2 ml saline in [group C] through infiltration in the anterior and posterior layer of the rectus sheath [transversalis fascia and parietal peritoneum], subcutaneous tissue and skin on upper and lower edges of surgical wound. At the end, neostigmine [0.04-0.06 mg/kg] and atropine [0.01 mg/kg] were used to counteract neuromuscular blockade. Women were sent to the post-anesthesia care unit [PACU] for a continued surveillance after extubation. HR and MAP were measured every 30 minutes post-operative until the patient was discharged from [PACU]. VAS was used to assess pain at 1,2,3,4,6,8,12,18, and 24 h postoperatively. Visual analogue scale  $\geq 4$  was treated with meperidine 0.5 mg/kg intravenous.

The time of the first analgesic request, total dose of analgesic consumption per 24 hours, time to start movement, breast-feeding, eating and passing flatus or stool and side effects of medications were recorded [nausea, vomiting, bradycardia and hypotension]. Heart rate  $< 60$  b/min was managed by intravenous atropine [0.5 mg]. MAP drops  $> 20\%$  of baseline value was managed by intravenous fluid and intravenous ephedrine 6-12 mg. Ondansetron 4 mg was used to treat nausea and vomiting.

Statistical analysis

The data was collected and analyzed by IBM SPSS v23 [Armonk, NY, USA]. The mean, standard deviation [SD] and median Interquartile range [IQR] were used to express quantitative data. Qualitative information presented as a number or %. The One-Way ANOVA test was used to compare more than two groups using quantitative data and parametric distribution, with post hoc

analysis by least significant differences [LSD]. While Kruskal Wallis test was used for data with a non-parametric distribution. Confidence interval 95% and error margin 5%. Statistical significance if P value less than 0.05.

RESULTS

In this study, 126 women were assessed for eligibility, 29 women did not meet the criteria and 7 women refused to participate in the study. The remaining 90 women were randomly assigned to three equal groups. The demographic data and the duration of surgery were comparable between groups being studied [P-value  $> 0.05$ ], as shown in table 1.

Table [2] reveals significant increase in the time of the first analgesic request in group A [8.4  $\pm$  1.91 h] and group B [7.5  $\pm$  1.81 h] than group C [4.3  $\pm$  1.24 h]. A significant decrease in pethidine consumption in group A [59.0  $\pm$  28.93 mg] than group B [72.0  $\pm$  23.1 mg] and group C [102.0  $\pm$  16.9 mg].

The visual analogue scale was significantly reduced in group A and B than in group C, but group A was superior [Table 3].

Table [4] is showing a reduction in the time of start breast-feeding, passing flatus or stool, start of eating and movement in group A and group B than in group C.

Table [5] demonstrates that group B had much more bradycardia than group A and group C [P=0.003], whereas no significant difference was detected for nausea and vomiting or hypotension.

Table [1]: The demographics of the study groups.

Variable		Group [A]	Group [B]	Group [C]	Test value	P-value	Sig
		No. = 30	No. = 30	No. = 30			
Age [years]	Mean $\pm$ SD	29.40 $\pm$ 5.37	30.47 $\pm$ 5.89	30.43 $\pm$ 5.63	0.347	0.708	NS
	Range	21 - 40	20 - 39	21 - 40			
Weight [kg]	Mean $\pm$ SD	72.13 $\pm$ 8.31	69.63 $\pm$ 7.19	73.87 $\pm$ 8.27	2.156	0.122	NS
	Range	60 - 85	60 - 83	61 - 85			
Height [cm]	Mean $\pm$ SD	163.80 $\pm$ 4.10	163.27 $\pm$ 4.73	161.90 $\pm$ 4.54	1.446	0.241	NS
	Range	157 - 170	156 - 170	155 - 169			
The duration of surgery [min]	Mean $\pm$ SD	44.67 $\pm$ 9.76	46.70 $\pm$ 10.08	47.17 $\pm$ 8.89	0.577	0.564	NS
	Range	30 - 60	31 - 60	31 - 60			

P-value  $< 0.05$ : Significant [S] •: One-Way ANOVA test. The information is displayed as [Mean  $\pm$  SD] and range.

Table [2]: Comparison of the three groups in terms of the first analgesic requirement and total pethidine consumption.

Variable		Group [A]	Group [B]	Group [C]	P value		
		The first analgesic requirement [h]	Mean $\pm$ SD	8.4 $\pm$ 1.91	7.5 $\pm$ 1.81	4.3 $\pm$ 1.24	$< 0.001^*$
	Range	6-12	5-10	3-6	P2	$< 0.001$	
					P3	$< 0.001$	
Total pethidine consumption [mg]	Mean $\pm$ SD	59 $\pm$ 28.93	72 $\pm$ 23.1	102 $\pm$ 16.9	$< 0.001^*$	P1	0.035
		Range	30-120	30-120		60-120	P2
						P3	$< 0.001$

P1: P value between group A and group B, P2: P value between group A and group C, P3: P value between group B and group C. P-value  $< 0.05$ : Significant.

Table [3]: Comparison among the three groups with respect to VAS

VAS		Group [A]	Group [B]	Group [C]	Test value	P-value	P1	P2	P3
1hr	Median [IQR]	0 [0 – 1]	0.5 [0 – 1]	1 [0 – 3]	1.813	0.043	0.315	0.021	0.037
2hr	Median [IQR]	0 [0 – 1]	0.5 [0 – 2]	2 [1 – 3]	2.215	0.033	0.214	0.042	0.038
3hr	Median [IQR]	1 [0 – 2]	1 [0 – 3]	3 [2 – 4]	2.452	0.021	0.715	0.007	0.032
4hr	Median [IQR]	1 [0 – 2]	2 [1 – 3]	3 [2 – 5]	4.315	0.007	0.072	0.011	0.027
6hr	Median [IQR]	2 [1 – 3]	3 [2 – 4]	4 [3 – 6]	5.215	0.001	0.213	0.001	0.021
8hr	Median [IQR]	2 [1 – 3]	3.5 [3 – 5]	5 [4 – 7]	4.325	0.027	0.412	0.009	0.017
12h	Median [IQR]	4 [3 – 6]	5 [4 – 7]	6 [5 – 7]	2.314	0.031	0.089	0.037	0.092
18h	Median [IQR]	3 [1 – 3]	3 [2 – 4]	3 [2 – 4]	1.123	0.321	0.514	0.413	0.364
24h	Median [IQR]	3 [2 – 5]	3 [2 – 5]	3 [2 – 5]	0.762	0.613	0.614	0.346	0.369

P-value <0.05: Significant [S], P1: Comparison between group A and group B, P2: Comparison between group A and group C and P3: Comparison between group B and group C.

Table [4]: Comparison between the three groups regarding the time of start breast-feeding, passing flatus or stool and start of eating and movement.

Variable		Group [A] No. = 30	Group [B] No. = 30	Group [C] No. = 30	Test value	P-value	Sig.
Time of start breast-feeding [h.]	Mean±SD	3.33 ± 1.21	3.67 ± 1.03	4.57 ± 1.19	9.262	0.000	HS
	Range	2 – 5	2 – 5	3 – 6			
Time of passing flatus or stool and start of eating [h.]	Mean±SD	4.63 ± 1.75	5.23 ± 2.14	6.23 ± 1.79	5.401	0.006	HS
	Range	2 – 7	2 – 8	3 – 9			
Time of start movement [h.]	Mean±SD	3.53 ± 1.17	3.83 ± 0.99	4.63 ± 1.16	7.917	0.001	HS
	Range	2 – 5	2 – 5	3 – 6			
Post hoc Analysis by LSD test							
Parameters					P1	P2	P3
Time of starting breast-feeding [h.]					0.264	0.003	0.000
Time of passing flatus or stool and start of eating [h.]					0.226	0.045	0.002
Time of start movement [h.]					0.297	0.006	0.000

P-value <0.05: Significant [S], P1: P value between group A and group B, P2: P value between group A and group C and P3: P value between group B and group C.

Table [5]: Adverse effects of medications in the study group.

Variable	Group [A]		Group [B]		Group [C]		Test value*	P-value	Sig.
	No.	%	No.	%	No.	%			
Nausea	3	10.0%	3	10.0%	4	13.3%	0.225	0.894	NS
Vomiting	1	3.3%	1	3.3%	2	6.7%	0.523	0.770	NS
Bradycardia	0	0.0%	7	23.3%	1	3.3%	11.799	0.003*	HS
Hypotension	0	0.0%	2	6.7%	2	6.7%	2.093	0.351	NS

P-value <0.05: Significant [S]. The information is displayed as number [%].

**DISCUSSION**

Effective postoperative analgesia can prevent hormonal, metabolic and cardiovascular responses to the stress of surgery and postoperative pain [9].

Although, the gold standard for pain relief is an opioid, it increases postoperative nausea and vomiting and slow the gastrointestinal motility's recovery [10].

Local anesthetics wound infiltration is an easy, effective and costless technique can enhance postoperative analgesia for different types of operations without major complications [6].

This study was designed to assess the efficacy of ketamine and dexmedetomidine in local wound infiltration on pain relief in patients underwent cesarean section.

Regarding the time to the first request analgesia, it was longer in group A and group B than in group C. This reflects the efficacy of ketamine and dexmedetomidine to provide adequate and extensive analgesia in local wound infiltration, which may be attributed to the synergistic effect of these drugs on combination with bupivacaine, but ketamine provided the longest time with superior analgesia. A significant decrease in total pethidine consumption in group A than group B and group C had been reported.

In agreement with our results, Mohamed *et al.* [8] reported prolonged time to the first analgesic request and less morphine consumption in ketamine and dexmedetomidine groups compared with the control group in major abdominal cancer surgery.

The results of our study were in accordance with the result of Kaler *et al.* [11] who reported prolonged time for the

first rescue analgesia in the ketamine group, with reduced total opioid consumption in lower segment cesarean section.

Also, Mitra *et al.* [12] found a longer time to the first rescue analgesia in the dexmedetomidine group, and less diclofenac consumption in lumbar discectomy surgeries.

In line with our findings, Garg *et al.* [13] reported that pain-free periods were longer with the ketamine & dexmedetomidine group than the control group with a significant decrease in the total analgesia required in spine surgery.

In agreement with our results, Ülgey *et al.* [14] found that dexmedetomidine reduced time of rescue analgesic and total morphine consumption in total abdominal hysterectomy.

On the contrary, Medhat *et al.* [15] reported no difference between the study groups regarding the time of the first analgesic request and opioid consumption in the subcostal transversus abdominis plane block in laparoscopic cholecystectomy. This may be attributed to the use of a small dose of ketamine [0.5 mg/kg] while we used [2 mg/kg] in our study.

Regarding visual analogue scale, it was significantly reduced in group A & B than group C, but ketamine was associated with superior analgesia.

In agreement with these findings, Mohamed *et al.* [8] reported a significant reduction in visual analogue scale in ketamine and dexmedetomidine groups than the control group in abdominal hysterectomy.

In addition, Tuchscherer *et al.* [16] demonstrated that ketamine [2mg/kg] subcutaneous infiltration provides adequate analgesia with lower visual analogue scale after cholecystectomy.

Also, Azemati *et al.* [17] concluded that an addition of dexmedetomidine to ropivacaine infiltration decreased post-inguinaherniorrhaphy pain without side effects.

Liu *et al.* [18] concluded that local anesthetic wound infiltration alone without adjuvants provides short-time analgesia postoperatively.

On the contrary, Medhat *et al.* [15] reported that insignificant difference was found between bupivacaine versus bupivacaine ketamine groups regarding visual analogue scale after laparoscopic cholecystectomy.

In the current study, early time of starting breast-feeding, time of passing flatus or stool and start of eating and time of starting movement were significantly higher among ketamine and dexmedetomidine groups than the control group.

Kaler *et al.* [11] reported that local anesthetic wound infiltration provides early ambulation, breast-feeding and passing flatus in the ketamine plus levobupivacaine group more than the levobupivacaine alone group.

Mohamed *et al.* [8] reported an insignificant difference among ketamine and dexmedetomidine groups regarding the time of starting movement.

Regarding side effects of medication, we observed 7 patients [27%] with bradycardia in group B versus one patient [4%] in group C while nil in group A. This could be attributed to the fact that dexmedetomidine has central inhibition of sympathetic outflow and decrease of noradrenaline leading to bradycardia and hypotension [19].

No statistically significant difference was reported regarding nausea, vomiting, hypotension, dizziness, or hallucination.

Mohamed *et al.* [8] concluded that there were insignificant differences among the studied groups regarding side effects.

Garg *et al.* [13] demonstrated few patients in the ketamine group had nausea, dizziness, and diplopia, but statistically insignificant.

**Conclusion:** Ketamine in local wound infiltration was superior to dexmedetomidine as ketamine increased time to the first analgesia required and decreased total analgesic consumption.

#### Conflict of interest

All authors declare that there was no possible conflict of interest.

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# International Journal

The background of the cover is a light blue gradient. It features a faint, semi-transparent graphic of a stethoscope on the left side, a globe in the center, and a white ECG (heart rate) line running across the bottom. The overall theme is medical and global.

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