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Postoperative Analgesic Effect of Using Bupivacaine Versus Bupivacaine with Dexmedetomidine or Ketamine in Cesarean Section Operations

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ABSTRACT

Background: Indeed, local anesthetic infiltration of surgical wounds is a straightforward, effective, and inexpensive approach of providing excellent postoperative analgesia for a wide range of surgical operations with minimal risk of adverse consequences.

Objective: The purpose of this study was to evaluate the efficacy of bupivacaine, bupivacaine combined with dexmedetomidine, or ketamine for post-operative analgesia following caesarean delivery.

Subjects and Methods: A total of 90 pregnant women scheduled for elective cesarean section, were equally divided into 3 equal groups (thirty each); **control (C) group:** received local wound infiltration with 40 mL of 0.25% bupivacaine (20 ml bupivacaine 0.5 %- and 20-ml saline) in two divided doses; **dexmedetomidine (D) group:** received local wound infiltration with a volume of forty mL of 0.25% bupivacaine plus 2 ug/kg dexmedetomidine; and **ketamine (K) group:** Patients had volume-specific local wound infiltration with forty ml of 0.25% bupivacaine plus 2 mg/kg ketamine.

Results: When compared to the other two groups, the ketamine group had a significantly longer duration before they needed analgesia ($P < 0.001$). Morphine consumption in the ketamine group was much lower than in the other two groups. ($P < 0.001$). The ketamine group had the most satisfied patients compared to the other two ($P < 0.001$).

Conclusion: It could be concluded that adding ketamine with bupivacaine in wound infiltration has a better effect than adding dexmedetomidine as regards hemodynamics stability, the time to the first analgesic request, patients' satisfaction, and the total dose of morphine consumption during the 24 hours post operatively.

Keywords: Bupivacaine, Dexmedetomidine, Ketamine, Cesarean Section.

INTRODUCTION

Cesarean section-related pain is the most debilitating side effect (CS). The best post-CS analgesic regimen should be effective while minimizing drug transfer through breast milk, and compromising the mother's capacity to care for the newborn [(1)]. The infusion of a local anesthetic into a wound is a simple, low-risk method of delivering postoperative analgesia following a variety of surgical procedures [(1)].

Anesthetic infiltration and continuous infusion into surgical wounds have been reintroduced in recent years as part of multimodal analgesia systems for postoperative pain control [(2)].

Different analgesic techniques have been discovered, such as: the transversus abdominis plane (TAP) block, local anesthetic wound infiltration, NSAIDs, iliaoinguinal-iliohypogastric nerve blockade, intrathecal additions, epidural analgesia, ketamine and finally gabapentin [(1)].

As a local anesthetic, Bupivacaine is often utilized because it has a longer duration of action, and a favorable sensory-motor neural block ratio. Neuronal depolarization can be prevented by bupivacaine binding intracellularly, and blocking to sodium input into nerve cells. Conversion to glucuronic acid in the liver is the primary mode of metabolism for amide group local anesthetics like bupivacaine [(3)].

Dexmedetomidine's broad-spectrum (sedative, analgesic, and anesthetic sparing) properties have garnered a great deal of interest and make it a beneficial, and safe, complement to many therapeutic applications in the medical sector. The analgesic properties of this drug are enhanced by intravenous, intramuscular, intrathecal, epidural, and perineural administration [(4)].

To alleviate post-operative pain, ketamine acts as a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor by inhibiting central sensitization [(4)].

The purpose of this work was to evaluate of the relative efficacy of bupivacaine, bupivacaine combined with dexmedetomidine, or ketamine for postoperative analgesia following caesarean sections.

SUBJECTS AND METHODS

This interventional comparative prospective controlled clinical study included a total of 90 pregnant women asking for general anesthesia for elective cesarean section, performed at the Department of Anesthesia, Surgical Intensive Care and Pain Management, Zagazig university hospitals.

The pregnant women were selected from the Obstetrics and Gynecology Department, Zagazig university hospitals. The selection was based on inclusion, exclusion criteria.

Inclusion criteria: The eligibility for the study was based on criteria of American Society of Anesthesiologists (ASA) criteria for physical status I, II. Subjects were aged 21-35 years and BMI was18-25 kg/m^2.

Exclusion criteria:

High risk pregnancies, emergency cases, and any medical condition that require a modification of the

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anesthesia protocol (e.g. hepatic diseases, renal diseases, cardiac patients, and history of allergy to study medications).

The included subjects were randomly divided into three groups (each thirty subjects). To ensure anonymity, the computer-generated table, was used to randomize these women. **Control group (Group C):** A local wound infiltration was performed to patients with forty mL of 0.25% bupivacaine (twenty ml bupivacaine 0.5 % and twenty ml saline) in 2 divided doses (i.e. twenty mL side of line of incision). **Dexmedetomidine group (Group D):** A local wound infiltration was performed to patients with 40 mL of forty mL of 0.25% bupivacaine plus two ug/kg dexmedetomidine (twenty mL for each side of lines of incision). **Ketamine group (Group K): bupivacaine.** A local wound infiltration was performed to patients with forty ml of 0.25% bupivacaine plus two mg/kg ketamine (twenty mL for each side of lines of incision)

All pregnant women were subjected to:

- Full history taking including age, medical, and history of previous operations.
- Routine laboratory investigations.
- Fasting before operations (6-8 hours). Before general anesthesia, IV line was inserted, full monitoring including, heart rate, mean arterial blood pressure, ECG, and respiratory rate were recorded (as base line readings). Intravenous 2 mg/kg propofol was used to produce general anesthesia, and then Controlled mechanical ventilation was started with a tidal volume of 7 ml/kg and to assist rapid sequence intubation, 0.6-1.2 mg/kg IV rocuronium was administered after the patient's breathing rate was carefully regulated to maintain an end-tidal carbon dioxide value of 30–35 mmHg. A continuous inhalational anesthetic depth of 0.5 MAC was maintained with isoflurane, and intravenous rocuronium doses of 0.1-0.2 mg/kg were used.

These individuals were randomly assigned to receive: (i) Control group (Group c): wound infiltration with bupivacaine only. (ii) Dexmedetomidine group (Group D): wound infiltration with bupivacaine, and dexmedetomidine group. (iii) Ketamine group (Group K): wound infiltration with bupivacaine, and ketamine group. In a sterile manner, Anesthesiologists prepared the medicines under study for local wound infiltration in sterile syringes prior to skin closure. Patients reversed by neostigmine 0.05 mg /kg with atropine 0.01 mg /kg at the end of the operation. IV paracetamol was given to all patients immediately following surgery, and then every eight hours thereafter

Data collection included:

Patients' characteristics: age, weight, height, ASA and BMI. Intra operative Hemodynamic parameters. Heart rate, noninvasive mean arterial pressure, and respiratory rate were recorded before induction of anesthesia, and every 10 min until the end of surgery. Mean arterial blood pressure, heart rate, respiratory rate, and visual analogue scale were evaluated at the recovery room immediately post operatively, then at 2, 4, 6,8,10, 12and 24 hours post operatively. The time to the first analgesic request was recorded. It was defended as the time from recovery until VAS greater than 3. Total dose of morphine requirement in 1st 24 hrs. Visual analog scale (VAS) was also noticed, which ranges: From 0 = no pain to 10 = worst imaginable pain which was used to asses post-operative pain at rest (VAS-R), as well as on coughing (VAS-M) at the following times: at the recovery room, immediately post operatively, and at 2, 4, 6, 8, 10, 12, and 24 hours post operatively. The patients were evaluated with a questionnaire about the 10-point scale to assess the patient's satisfaction about analgesia post operatively (as, 0= no satisfaction to 10= fully satisfaction)**.**

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (ZU-IRB #7092). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In order to analyze the data acquired, Statistical Package of Social Services version 20 was used to execute it on a computer (SPSS), and to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) was used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X2) were also, used to assess qualitatively independent data. The significance of a P value of 0.05 , or less was determined.

RESULTS

Age was distributed respectively with no statistically significant differences among groups. Also there were no statistically significant differences regards BMI, or ASA distribution ($p > 0.05$) (table1).

Table (1): Demographics and characters of the studied patients

			Group C (N=Thirty)	Group D (N=Thirty)	Group K (N=Thirty)	X^2/ F	P
Age (years)			29.36±4.23	28.63±5.23	27.45±4.12	1.702	0.182
Weight (kg)			72.52±12.63	74.96±18.63	75.85±16.32	0.965	0.325
Height (cm)			167.16±17.25	166.95±11.36	167.01±9.36	0.885	0.412
BMI (kg/m^2)			23.95±3.02	24.28±4.71	25.19±3.85	2.354	0.125
ASA	**I**	**N**	20	25	23		
		%	66.7%	83.3%	76.7%		
	II	**N**	10	5	7	2.28	0.31
		%	33.3%	16.7%	23.3%		
Total		**N**	30	30	30		
		%	100.0%	100.0%	100.0%		

N: Number BMI: Body Mass Index ASA: American Society of Anesthesia.
Group C; Control group, Group D: Bupivacaine, Dexmedetomidine group and Group K: Bupivacaine, ketamine group
P > 0.05 was considered non-significant.

Between the ages of 10 and 60, Group D had a significantly lower HR than any of the other two groups.($p < 0.0001$), regarding other time periods , The differences between the three groups were not statistically significant.($p >0.05$) (Table 2).

Table (2): Heart rate distribution among the patients

	Group C (N=Thirty)	Group D (N=Thirty)	Group K (N=Thirty)	F	P
HR basal beat/min	80.12±2.21	82.98±1.85	79.21±1.51	1.423	0.211
HR_10 min	74.22±2.41	65.36±4.52*	74.99±7.56	12.856	0.00**
HR_15 min	74.11±3.25	62.65±6.86*	75.63±8.69	16.568	0.00**
HR_30 min	75.21±5.12	63.22±5.23*	76.85±11.32	17.235	0.00**
HR_45 min	74.19±6.21	66.81±7.52*	75.25±5.28	11.541	0.00**
HR_60 min	74.36±7.25	68.79±6.25*	74.36±5.85*	8.388	0.00**
Immediately post-operative	74.11±2.4	71.21±7.55	74.63±8.87*	2.554	0.068
HR_post2H	74.85±2.46	72.87±4.59	75.85±8.07*	2.452	0.079
HR_post4H	78.36±10.23	75.53±9.23	76.83±7.52	1.884	0.212
HR_post6H	77.36±7.43	76.53±9.43	76.73±7.62	1.574	0.312
HR_post8H	77.33±3.58	75.37±2.33	76.87±7.52	1.454	0.289
HR_post10H	77.36±10.43	75.73±9.23	77.83±7.62	1.784	0.232
HR_post12H	77.55±6.25	76.51±4.61	77.37±5.85	0.125	0.895
HR post 24H	76.54±1.95	75.54±1.66	76.15±3.06	0.085	0.902

At 2 Hs, Group C had a significantly higher VAS than the other two groups, and at 12 Hs, there was no difference between the groups, and at 24 Hs, there was no difference among the three groups (Table 3).

Table (3): Visual Analogue Scale during rest at different times among the groups

	Group C (N=Thirty)	Group D (N=Thirty)	Group K (N=Thirty)	Kruskal Wallis	P
Immediately post-operative	4.0 (1-6) *	1.0 (0-2)	0.0 (0-1)	58.63	0.00**
VAS2	3.0 (1-5) *	0.0 (0-2)	0.0 (0-1)	54.411	0.00**
VAS4	3.0 (2-6) *	1.0 (0-2)	1.0 (0-2)	27.663	0.00**
VAS6	3.0 (2-7) *	2.0 (0-3)	1.0 (0-3)	24.362	0.00**
VAS8	4.0 (2-5) *	2.0 (0-4)	2.0 (1-4)	35.186	0.00**
VAS10	4.0 (3-5) *	2.0 (0-4)	2.0 (0-4)	34.176	0.00**
VAS12	4.0 (3-5) *	2.0 (1-4)	2.0 (0-3)	28.271	0.00**
VAS24	3.0 (2-4)	3.0 (1-4)	2.0 (1-4)	2.034	0.154

VAS: Visual Analogue Scale. $p < 0.0001$ was considered significant compared to the other two groups.

With no statistically significant differences between groups A and B, VAS was significantly higher in Group C from 2 Hs tell the 12 Hs than in the other two groups, and also, In the table, we can see that there is no statistically significant difference between the three groups in terms of 24 Hs. Time to first analgesic request was significantly longer in the K group than in the other two groups..($p < 0.001$). In addition, as compared to the other two groups, group K consumed much less morphine in the 24 hours following surgery.($p < 0.001$) **(Table 4).**

Table (4): Visual Analogue Scale during cough at different times among groups

	Group C (N=Thirty)	Group D (N=Thirty)	Group K (N=Thirty)	Kruskal Wallis	P
Immediately post-operative	5.0 (2-7) *	2.0 (1-3)	1.0 (1-2)	35.63	0.00**
VAS2	5.0 (2-6) *	2.0 (1-3)	1.0 (1-2)	39.631	0.00**
VAS4	4.0 (2-6) *	1.0 (1-3)	1.0 (0-2)	22.514	0.00**
VAS6	4.0 (2-7) *	2.0 (1-4)	2.0 (0-3)	20.854	0.00**
VAS8	4.0 (2-5) *	2.0 (0-4)	2.0 (1-4)	32.521	0.00**
VAS10	4.0 (2-6) *	2.0 (1-4)	2.0 (1-4)	33.541	0.00**
VAS12	5.0 (3-7) *	3.0 (1-5)	2.0 (1-4)	14.365	0.00**
VAS24	4.0 (2-6)	4.0 (2-6)	3.0 (2-5)	1.8954	0.154

VAS: Visual Analogue Scale. $p < 0.0001$ was considered significant compared to the other two groups.

Time to first analgesic request was significantly longer in the K group compared to the other two groups ($p < 0.001$). Also group K had significantly the lowest dose of morphine consumption during 24 hours post operatively relative to the other two groups ($p < 0.001$) table No significant difference or association except bradycardia as it was significantly associated with Group D **(Table 5).**

Table (5): Patient satisfaction, morphine use, and the time to the first analgesic request were all measured in the various groups.

			Group C (N=Thirty)	Group D (N=Thirty)	Group K (N=Thirty)	F	P
The time to the first analgesic request (h)			5.13±0.81#	7.83±0.74	9.20±1.21*	228.66	0.00**
The total dose of morphine used over 24 hours (mcg)			75.66±31.62*	55.33±21.63	35.50±13.85#	21.34	0.00**
Patient satisfaction	**Not**	**N**	10	5	3		
		%	33.3%	16.7%	10.0%		
	Average	**N**	15	10	5	23.011	0.00**
		%	50.0%	33.3%	16.7%		
	Good	**N**	5	15	22		
		%	16.7%	50.0%	73.3%		
Total		**N**	30	30	30		
		%	100.0%	100.0%	100.0%		

H: Hour. P <0.001 was considered significant when compared with the other two groups.

There was no significant difference or association was noticed, except bradycardia which was significantly associated with Group D (**Table 6**).

Table (6): Complications among studied groups

		Group			X^2	P
		Group C (N=Thirty)	Group D (N=Thirty)	Group K (N=Thirty)		
Nausea	**N**	4	3	8	3.36	0.18
	%	13.3%	10.0%	26.7%		
Vomiting	**N**	5	1	5	3.31	0.19
	%	16.7%	3.3%	16.7%		
Shivering	**N**	2	1	5	3.56	0.16
	%	6.7%	3.3%	16.7%		
Bradicardia	**N**	3	11	4	7.91	0.019*
	%	10.0%	36.7%*	13.3%		
Hypotension	**N**	3	3	4	0.22	0.89
	%	10.0%	10.0%	13.3%		
Total	**N**	30	30	30		
	%	100.0%	100.0%	100.0%		

DISCUSSION

With a recent reported overall cesarean section rate of 54% in Egypt, cesarean delivery is a common obstetric procedure that causes moderate to severe postoperative discomfort. Postoperative analgesia can be enhanced through infiltration of the wound site with an analgesic agent [5, 6]. When it comes to post-operative pain management, local anesthesia injections are an excellent choice because they don't pose any significant risks [7,8].

Bupivacaine, Dexmedetomidine, and ketamine were all employed in this study for postoperative analgesia following caesarean section, and the results showed that ketamine had a better effect on hemodynamic stability than Dexmedetomidine, first analgesic request, patient satisfaction, and morphine consumption in the first 24 hours after surgery.

Garcia *et al.* [9] reports that wound infiltration with local anesthetics plus either ketamine or dexmedetomidine increases the duration until the first request for analgesia while decreasing overall analgesic intake, with ketamine being deemed preferable.

According to the findings of **Jha and his colleagues** [10], injection of bupivacaine or ketamine into the surgical incision gives appropriate analgesia and is free of severe adverse effects. Compared to bupivacaine, ketamine is better in relieving pain, promoting a restful sleep, and allowing patients to resume eating sooner after treatment.

In the present study, HR was significantly lower among Group Dexmedetomidine from 10 min tell the 60 minutes compared to the other two groups, regarding other times, with no significant differences among the groups .

This finding corroborated the findings of **Mohamed *et al.*** [4], who found that dexmedetomidine binds to receptors in the medullary vasomotor center, decreasing the turnover of norepinephrine and decreasing central sympathetic outflow via the medullospinal nor adrenergic pathway.

This study showed significantly lower VAS score during rest and cough in ketamine and dexmedetomidine groups up to12 hrs. postoperatively compared to control group.

This result was in accordance with, **Mohamed *et al.*** [4] who found that ketamine and dexemetomedine reduced postoperative pain levels compared to group bupivacaine.

Also, this result agreed with, **Kang** [11] in patients who had inguinal herniography, they observed that dexmedetomidine and ropivacaine infiltration greatly reduced postoperative pain.

In this study, as regard the time to first analgesic request, it was significantly longer in K group (ketamine group) when compared with the other two groups.

This coincides with, **Mohamed *et al.*** [4]; who found that patients who received ketamine, or dexmedetomidine in addition to bupivacaine for local wound infiltration had a considerably longer delay to the first request for rescue analgesia, compared to group D and group C, after they underwent total abdominal hysterectomy.

In the present study, ketamine group had significantly the lowest dose of morphine consumption during 24 hours post operatively compared with the other two groups.

This conclusion was consistent with the findings of **Mohamed *et al.*** [4], who observed that PCA morphine consumption was considerably lower in group K compared to groups D and C, with no significant difference between K and D.

Singh and Prasad [12] found that Dexmedetomidine patients had lower morphine use after complete abdominal hysterectomy compared to the control group.

In the current study, there was highly significant difference between studied groups as

regards patients' satisfaction, as patients in ketamine and dexmedetomidine groups had higher satisfaction rate compared to Control group, however, the ketamine group was the superior in patients' satisfaction.

This result was in agreement with**, Singh and Prasad** [(12)] who found that more patients in the dexmedetomidine group than in the control group were satisfied with the treatment.

In the current study, as regards complications (i.e., Nausea, vomiting, shivering, or hypotension) there was no significant difference among groups except bradycardia which was significantly associated with group D (dexmedetomidine group).

These results agreed with, **Mohamed *et al.*** [(4)] in which they found no significant differences in the occurrence of additional adverse effects between the three groups tested.

Singh and Prasad [(12)] both groups were found to have a minor incidence of post-operative hypotension. It was found that neither the control group nor the dexmedetomidine group experienced any other side effects during abdominal hysterectomy.

CONCLUSION

It could be concluded that adding ketamine with bupivacaine in wound infiltration has a better effect than adding dexmedetomidine as regards hemodynamic stability, the time to first analgesic request, patients' satisfaction, and the total dose of morphine consumption during the 24 hours post operatively.

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