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Analgesic and Opioid Sparing Effects of Tramadol, Ketamine, and Bupivacaine Following Wound Infiltration After Caesarean Section

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Abstract: *Background:* Adequate management of pain is considered a fundamental human right and social justice and this may be achieved for women who had caesarean section under subarachnoid block with multi modal means of analgesia. Wound infiltration with different agents may be part of the multi modal means of providing adequate analgesia. The study aimed to determine which of plain bupivacaine, ketamine or tramadol will give the best pain control post-operatively in terms of quality and duration of pain relief when used for wound infiltration following caesarean section under subarachnoid block. *Methods:* A prospective double blind randomized study of 132 patients, divided into three groups of A, B, and C with 44 patients in each group. Each group had wound infiltration with either 0.125% plain bupivacaine (Group A), 0.25% ketamine (Group B), or 0.25% tramadol (Group C) after caesarean section under subarachnoid block. Pain was assessed hourly in the first 4 hours then 4 hourly for 20hours. The duration of pain relief after subcutaneous infiltration, morphine consumption, and side effects were noted for all the three groups. *Results:* Time to first rescue analgesic was similar in all three groups, however duration of analgesia was longest in Group A (4 hours). ANOVA analysis of the time to first analgesic request across the three groups was not statistically significant (p=0.0862). Morphine consumption was highest in Group C with an average of 7mg in 24 hours, but was lower in Groups A and B which were 5.09mg and 5.63mg respectively in 24 hours. Using the 5 point Likert to test for patient satisfaction; group A recorded highest percentage of patients who strongly agreed to being satisfied, while the least percentage to satisfaction was found in Group C. *Conclusion:* This study demonstrated that of the three drugs tested, bupivacaine was the most effective analgesic with consequent reduction in opioid consumption and offered prolonged patient satisfaction.

Keywords: Wound Infiltration, Bupivacaine, Ketamine, Tramadol, Caesarean Section

1. Introduction

The prevalence of post-operative pain has been described by several authors and up to 77% of patients complain of pain with 80% of these patients experiencing moderate to severe pains. [1, 2] Nwasor et al. reported moderate pain in 34.8% and mild pain in 65.2% of surgical patients 8 hours after the operation before subsequent doses of analgesia were given. [1] Kolawole and Fawole pointed out that the first 24 hours post-operatively was particularly painful for patients with 79.6% and 54.6% reporting moderate to severe pain in the recovery room and on day one respectively. [2] Optimal pain relief in the mother permits early mobilization, prompt bonding with the neonate, early initiation of breast feeding, prevention of postpartum depression and

prevention of chronic pain syndromes in future. [3] Caesarean section is associated with moderate to severe post-operative pain. [2, 4] Management of post-operative pain following caesarean section is not adequate in our environment. [1, 2] To achieve no pain to mild pain after caesarean section, multimodal analgesia is usually required to provide high-quality analgesia. [3] It also involves use of different anaesthetic methods.

Various drugs are used for surgical site infiltration, with local anaesthetic agents like lidocaine and bupivacaine being the most commonly used. [5] Other drugs that have local anaesthetic properties that are not commonly explored in our environment include opioids, ketamine, Alpha 2 agonist (e.g. clonidine, dexmedetomidine), and magnesium either as sole agents or as adjuvants. [6]

Infiltration with tramadol does not cause some of its known side effects which include headache, dizziness, constipation, nausea, itching, sweating etc. [7] Ketamine has many routes of administration which include oral, intravenous, intramuscular, epidural, and when its local anaesthetic property is required can be used for infiltration. [8, 9] There is a strong need to find ways of extending post-operative analgesia using agents with minimal side effects, and decreased need for opioid and its possible side effects such as drowsiness. Wound infiltration is one of the simplest forms of local anaesthesia which may form part of multimodal intervention to achieve optimal analgesia post-operatively. It is also convenient as it can be done easily with no special equipment required.

Ketamine and Tramadol were selected for this study for comparison with plain bupivacaine (normally used for wound infiltration to achieve longer duration of analgesia), because both drugs also have local anaesthetic properties. We aimed to assess the analgesic and opioid sparing effect using wound infiltration of plain bupivacaine, ketamine and tramadol following caesarean section.

2. Materials and Methods

Ethics and approval was obtained from the ethics and research board of the hospital. The study was carried out over a 10months period between 2019 and 2020. The sample size was calculated using the formula below:

Sample size formula for each group (n) is given by: [10]

$$\lambda = n\Delta;\ n = {}^{\lambda}/_{\Delta}$$

Where n = minimum sample size for each group
Δ = effect size,
λ = non-centrality parameter
At level of significance $\alpha = 0.05$

$$\text{Power} = 1 - \beta = 0.80$$

Using G"Power 3.0.10 statistical software to calculate effect size and non-centrality parameter
calculation of effect size (Δ) = 0,25
and non-centrality parameter (λ) = 9.94
substituting for the equation n = λ/n
9.94/0.25 =39.76 which was rounded up to 40 patients in each group. A 10% allowance was made for attrition in this study, thus 44 patients was needed in each group, making a total of 132 patients for all three study groups.

The study procedure was explained to each patient on the ward a day before surgery and informed consent was obtained.

In the operating room, the baseline haemodynamic parameters including pulse rate (PR), non-invasive blood pressure (NIBP), mean arterial blood pressure (MAP) respiratory rate (RR), and peripheral arterial oxygen saturation (SPO_2) were measured using MEDELA PM 400 modular monitor, GE Medical systems, Information, Technology, Inc.8200w. Tower Ave, Milwaukee, USA) capable of monitoring non- invasive blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP] and mean arterial blood pressure [MAP]), heart rate (HR), peripheral arterial oxygen saturation (SPO_2) and electrocardiography (ECG). The baseline parameters were taken and recorded when patient was supine with a Crawford wedge on the right hip. An intravenous access was obtained using a 16G cannula in a prominent vein in the forearm. Patients were preloaded with 15ml/kg of 0.9% normal saline over fifteen minutes before subarachnoid anaesthesia. [11]

The attending physician anaesthetist administered the spinal anaesthesia in accordance with the standard protocol for CS. Surgery was allowed to proceed after achieving a block height of thoracic dermatome of T6 while patient monitoring continued intraoperatively. Hypotension (MAP < 60 mmHg or a SBP of 25% < the patient's baseline value) was treated with intravenous 0.9% saline and ephedrine boluses (3 – 6 mg) titrated to effect.

Before closing the skin towards end of the surgery, the scrub nurse handed to the obstetrician a 20ml syringe containing either 0.125% plain bupivacaine, 0.25% ketamine or 0.25% tramadol prepared under aseptic condition by the pharmacist for infiltration of the skin.

Data presentation was with tables and figures. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 24. Summary statistic was displayed using mean and standard deviation for continuous variables while categorical variables were presented as percentages. Chi-square was used to test for association between categorical variables while Student t test and ANOVA were used to compare means of continuous variables. A P-value of < 0.05 was considered statistically significant.

2.1. Pain Assessment

Post-operative analgesia commenced 2 hours from the time of intrathecal injection, with all patients receiving intravenous paracetamol 1g and intramuscular diclofenac 75mg, and this continued 8 hourly and 12 hourly respectively for 24 hours after surgery.

Post-operative pain assessment using the numerical rating scale (NRS), commenced an hour after the subarachnoid block. In this scale, 0 corresponds to no pain, 1, 2, 3 mild pain, 4, 5, 6 moderate pain and 7, 8, 9, and10 reflects severe pain. Pain assessment was done at hourly intervals for the first 4 hours, then 4 hourly for the next 20 hours by the Researcher or

resident doctor blinded to the medication given for surgical site infiltration. Assessment of pain was not done when patient is asleep. Intravenous morphine 2mg or more was administered whenever there was a minimum score of 4 on NRS by the resident doctor. The total morphine consumed in 24 hours by each patient was recorded.

The potential toxicity of morphine was looked out for, by monitoring the respiratory rate, peripheral arterial oxygen saturation, proper dosage during bolus administration, as well close monitoring of the patient, especially the few hours post-operatively.

2.2. Outcome Measures

2.2.1. Primary Outcome

This was to find out which of the three drugs gave the longest duration of analgesia following surgical site infiltration with either plain bupivacaine, tramadol, or ketamine. First analgesic request was measured from the time of infiltration to when a minimum score of 4 was obtained on the NRS.

2.2.2. Secondary Outcome

The average amount of morphine consumed in 24 hours in all the three groups was also obtained.

Effects of the three drugs on opioid consumption, tolerability of these drugs in terms of drowsiness, nausea, and vomiting as well as patient's overall satisfaction using the Likert scale were obtained.

3. Results

A total of one hundred and thirty-two patients participated in the study with 44 patients in each of the three groups. The physical profile (age, weight, height and BMI) summary of all the groups were comparable as shown in Table 1.

Result of the block heights across the three groups is shown in Table 2, with majority of patients across the three groups having a block height of T6 or T7 following the subarachnoid block, translating to similar regression time.

3.1. Time to First Analgesic Request

Table 3 shows the comparison of time to first analgesic request between group A (bupivacaine group) and group B (ketamine group) and group C. Average time to first analgesic request for those in group A was 4 hours, while time to first analgesic request was 3.49 hours and 3.78 hours for patients in groups B and C respectively. Upon analysis using ANOVA, (P= 0.0862) was obtained which shows no statistical significance across the three groups in terms of mean time to first analgesic request.

Group A patients had the lowest need for rescue analgesia with mean morphine consumption of 5.09mg±1.52 in 24 hours. The highest morphine consumption was by patients in group C at 7.42mg±1.01 in 24 hours.

Figure 1 gave the trend in morphine consumption for all the 3 groups in 24 hours. Group A patients did not require morphine until after 2 hours post-operative. Morphine consumption increased steadily until it reached a peak at the fourth hour, then a gradual decline in demand until an abrupt halt at the tenth hour.

Patients in group B (ketamine group), demand for additional analgesic commenced 1 hour post-operative, with a steady rise in consumption of morphine to the third hour. This plateaued for another hour, then a gradual decrease from the fifth hour to the eighteenth hour, then remained level till end of 24 hours. For patients in group C request for morphine also started in the first hour postop like patients in group B. However, unlike the trend in group B patients, there was a sharp peak at the third hour, and a gradual decrease in demand for morphine till end of 24 hours period.

Group A patients did not require morphine until 2 hours postop whereas Groups B and C started at 1 hour postop to receive morphine, with a gradual reduction over time for morphine across all the three groups.

Group A patients did not require morphine after 10 hours postop whereas Group B had morphine up to 18 hours and Group C up to 24 hours post op.

Average morphine consumption in each patient was highest among Group C patients (7.42mg), followed by Group B (5.63mg) and was least in Group A (5.09mg). Analysing morphine consumption revealed P = 0.000, which was statistically significant.

Table 1. *Patients demographic characteristics in the three groups.*

Demography	Frequency			P-value
	Group A (Bupivacaine)	Group B (Ketamine)	Group C (Tramadol)	
Age (years)	30.30±6.24	29.67±5.52	28.31±5.12	0.239
Weight (Kg)	82.43±8.91	82.16±6.82	81.27±9.03	0.788
Height (m)	1.73±0.20	1.71±0.23	1.72±0.21	0.310
BMI (kg/m^2)	27.54±3.20	28.90±2.40	24.47±3.36	0.422
Marital Status				0.771*
Single	0	1	1	
Married	44	43	43	
Educational Status				0.534*
None	6	5	5	
Primary	2	6	3	
Secondary	3	7	7	
Tertiary	33	26	29	

Table 2. *Dermatomal block heights across the three groups.*

Group	Block Height			
	T6	T7	T8	T9
Bupivacaine (n=)	20	15	8	1
Ketamine (n=)	21	10	11	2
Tramadol (n=)	19	17	8	

Table 3. *Comparing time to first analgesic request across the three groups using ANOVA.*

Group	Mean time to first rescue analgesia (hour)	F- Value	P-value*
A (Bupivacaine)	4	2.989	0.0862
B (Ketamine)	3.49		
C (Tramadol)	3.78		

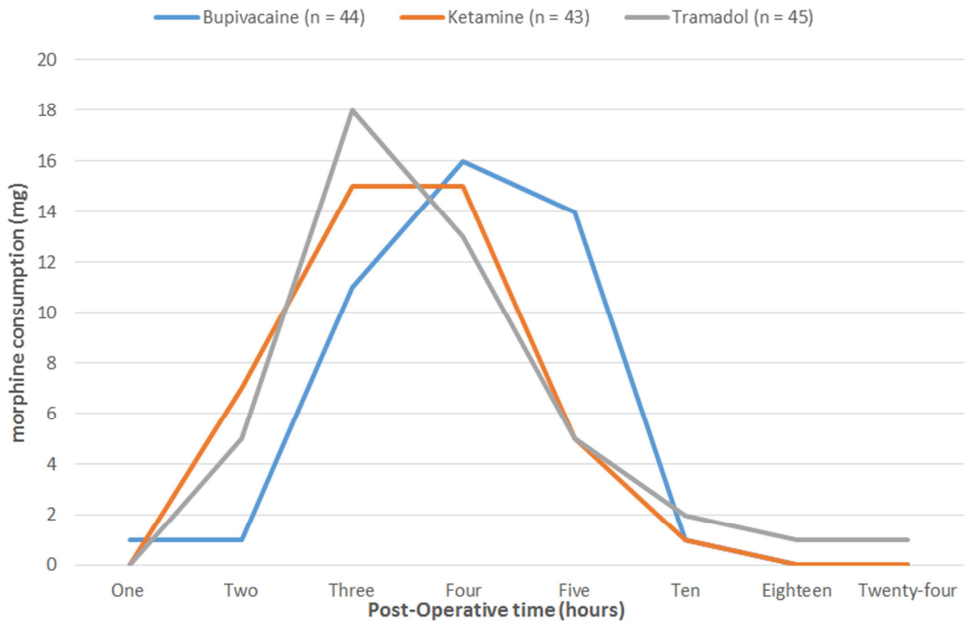

Figure 1. *Morphine Consumption within 24 Hours after surgery.*

4. Discussion

This study shows that duration of analgesia after skin infiltration with bupivacaine and opioid sparing effects was better than ketamine and tramadol. In addition, time to first analgesic request was similar in all the three groups, but was longest in group A patients which was not statistically significant.

Results of time to first analgesic request in each of these groups was in agreement with the studies by Warnicke et al, [12] Bahaeen et al [13] and Edomwonyi and colleagues, [14] who all reported similar time duration before first analgesic request. Bahaeen et al [13] reported 3.37 hours and 3.43 hours for Kpre group (ketamine infiltration before incision) and Kpost group (ketamine infiltration post-surgery) respectively. Edomwonyi and colleagues [14] reported a mean of 3 hours after infiltration with bupivacaine in their two study groups.

The agreement between index study and aforementioned studies in terms of time to first analgesic request may be due to similar concentration of bupivacaine used hence explaining the similarity in results reported.

This result in the index study is however in contrast to that of the study by Mohammad and colleagues, [15] who concluded that tramadol was more effective for infiltration than bupivacaine. This could be due to the higher dose of tramadol (2mg/kg), used in their study compared to 50mg of tramadol (0.25%) used in this study. Also what may have made bupivacaine less effective in the study of Mohammad and colleagues was the lower concentration used (0.025% of bupivacaine) compared to 0.125% of bupivacaine used in this study leading to the different conclusions reached between index study and that by Mohammad and his colleagues.

Sachidananda et al [16] came to a conclusion that a combination of tramadol with bupivacaine was better than bupivacaine alone for skin infiltration. This may be true given the report of synergism between local anaesthetic agents by other studies. Synergy is the interaction of two substances to produce a combined effect greater than the sum of their separate effects. Sachidananda et al also used a higher dose of tramadol 2mg/kg in their study.

Abdallah et al [17] as well as Abdullah and Waleed [18] concluded that ketamine or tramadol gave better analgesic control in their respective studies. However, these two studies groups also used higher doses of ketamine (2mg/kg) and tramadol (1mg/kg) respectively compared to this index study

in which 50mg (0.25%) of both tramadol and ketamine were used.

It could be suggested that higher doses of tramadol and ketamine may give better pain control and possibly increase the time to first analgesic request. Likewise, combinations of these drugs as well may act synergistically to increase the time to first analgesic request as reported by Sachidananda et al. [16] However these higher doses were associated with side effects such as drowsiness and nausea in their study.

This research also looked at the average morphine consumption as well as trend in morphine consumption in 24 hours in all the three groups in 24 hours. Morphine consumption was highest in group C patients (Tramadol group), because more bolus doses of morphine were needed to provide more effective analgesia. Groups A and B patients however needed less morphine to achieve a satisfactory pain score. In all the three groups peak demand in morphine consumption across the three groups was at the third and fourth hours from the time of infiltration, but need for morphine gradually reduced as the time progressed.

It was noticed that morphine consumption was lowest in group A patients (bupivacaine group) compared with the other two groups, this demonstrate the greater opioid sparing effect of bupivacaine when used for infiltration.

The lower pain scores in group A patients should be interpreted together with the morphine-sparing effect. The reason for less morphine request by Group A patients may be due to the high protein binding of bupivacaine leading to long duration of action of up to 8 hours. [19, 20] Durations of action of bupivacaine for 24 hours [22] have been reported leading to less morphine consumption.

Group B patients had ketamine as infiltrate, this group had morphine consumption similar to patients in Group A. The reduced morphine consumption may be related to the direct analgesic actions of ketamine mediated via the mu receptor and the inhibitory action of the excitatory glutamatergic NMDA receptors. Also this opioid sparing effect of ketamine noticed may also be due to the active metabolite norketamine. Prolonged analgesic action after a single injection may be due to ketamine's active metabolite norketamine; its anti-inflammatory effects, inhibition of nociceptive central hypersensitization and attenuation of acute tolerance to opiate administration have been reported. [19, 21]

Warnicke et al. [12] even postulated that analgesic effects of ketamine may last up to 1 week and beyond. However, this was not part of the set objectives of this study hence was not actively looked out for.

The trend of morphine consumption reported in this study was in contrast to that reported by Jabalameli et al, [23] who gave their results in percentages, but reported the highest morphine consumption in the placebo group; followed by the bupivacaine group, and then the tramadol group. The least morphine consumption was in pethidine group, and this may have been due to the higher dose of pethidine which was administered compared to that given to patients who had tramadol.

The same contrasting result was also obtained from the study by Abdullah and Waleed. [18] Although pethidine was used as rescue analgesic, the patients in the levobupivacaine group consumed more pethidine than patients in the ketamine group. However, when pethidine strength is adjusted to that of morphine used in index study, overall morphine consumption was smaller in this study across the three groups. This may be due to the differences in anaesthetic plan, where general anaesthesia was adopted for their study compared to neuro-axial block used in this study.

Block heights were similar across the three groups; this should translate to similar regression time across the three groups. Also similar doses of heavy bupivacaine were administered to all the patients, contributing to drug homogeneity. Therefore, any significant differences in post-operative analgesia may be due to the different agents used for infiltration.

5. Conclusion

This study demonstrated that skin infiltration with bupivacaine at surgical site was more effective than ketamine or tramadol in providing surgical site pain relief.

5.1. Limitation/ Challenges

It would have been nice to assay for the serum levels of the different drugs used for infiltration in this study, to evaluate the link between the blood concentration of these drugs and the resulting analgesic effects.

Also assay for stress markers such as serum cortisol, prolactin and glucose levels before surgery, at 6 and 24 h postoperatively if measured would better establish link between adequate analgesia and the different infiltrates. Unfortunately, due to time, equipment, and financial constraints this was not possible.

5.2. Recommendation

Bupivacaine is strongly recommended for skin infiltration following Caesarean section under subarachnoid anaesthesia as part of multi modal pain management. Surgical site infiltration with bupivacaine was found to be safe and effective.

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Conflicts of Interest

The authors declare no conflict of interest.

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