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Original article

Diclofenac-Tramadol Versus Diclofenac-Acetaminophen Combination for Post Caesarean Section Pain Control: A Randomized Controlled Trial

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Abstract

Background: Post-Caesarean section morbidity due to pain is a health concern to both the mother and the clinician. This is because good post-operative pain control helps early recovery and mother-baby bonding with early discharge. Various combinations aimed at this have not had any consensus unlike labour analgesia. This study is aimed at helping clinicians in decision making toward post cesarean pain analgesia. ***Methodology:*** This was a double-blinded randomized controlled trial following Caesarean section under spinal anesthesia over a 6month period. One hundred and seventy eligible participants were randomized into two groups. Group A received intramuscular Tramadol 100mg 8 hourly for 24 hours. Group B received intramuscular acetaminophen 600mg 8 hourly for 24 hours. Both groups received Rectal Diclofenac 100mg 8 hourly for 24 hours. The first dose of the drugs was administered one hour after the surgery. All the participants received 10mg of prophylactic metoclopramide. The outcome measures were post-caesarean pain score, participants' satisfaction and maternal side effects within the first 24 hours. The pain control was assessed using visual analogue scale while patients' satisfaction was assessed with Likert scale. ***Analysis:*** Absolute and relative frequencies of categorical variables, mean, range and standard deviation of continuous variables were calculated. Associations between continuous variables were analyzed using students t-test while chi-square ($\chi 2$) test (or Fisher's exact test where applicable) was used for categorical variables. A P-value of <0.05 was considered significant. ***Results:*** The overall pain score was statistically significantly in the diclofenac-tramadol group (P-value <0.001). The Acetaminophen group required more rescue analgesia (63.5% Vs 34.1%) and this was statistically significant (P-value <0.001). The level of association between the types of caesarean section and pain scores both at rest and with movement was statistically significant, with Tramadol group having better pain control. The composite scores in both groups, both at rest, with movement and the types of caesarean section were not statistically significant. On patients satisfaction, 67.1% of the diclofenac-tramadol group was very satisfied as against 30.6% in the diclofenac-acetaminophen group and was statistically significant (P-value = 0.001). The side effect profile was not significant between the two groups. However, the commonest side effects were Dizziness and nausea, which were more in the Tramadol group (10.6% Vs 7.1%). ***Conclusion:*** The diclofenac–tramadol combination was more effective in pain control with better patients' satisfaction and minimal side effects.

Keywords: ***Tramadol, Acetaminophen, Diclofenac, post caesarean analgesia, post-operative pain***

Introduction

Caesarean section involves the delivery of the baby after the age of viability through an incision made on the anterior abdominal wall and uterus. It is the second commonest obstetrics procedure after episiotomy [1-3]. It can be elective or emergency [1]. It becomes the route of delivery of choice when there is contra indication to vaginal delivery during pregnancy or complications in labour [2]. The rate of Caesarean section has been increasing worldwide [2-4] with a global rate of 10-35% [2]. It varies from country to country, and institution to institution [2-4]. In Sub-Saharan Africa, the recorded rate was 22% [5]. In Nigeria, the institutional based rates vary between 18.5% -

27.6% [5]. However in Abakaliki, the rate of caesarean delivery was 16.4% which is higher than the WHO rate [6,7].

Post-Caesarean section pain is one of the major challenges that hinder a satisfying postoperative period as Caesarean section produces moderate to severe pain in the first 24 to 48 hours [9,10]. Any intervention done to relieve it will make the women have a good postoperative experience [1]. It contributes to the various reasons for aversion for caesarean section [8]. This may interfere with the patient's ambulation, breastfeeding, and early maternal bonding with the infant [11,12] and increases risk of venous thromboembolism [12]. However, adequate postoperative analgesia averts/reduces the risk of these complications [10-12]. An ideal post-Caesarean analgesic regimen must be cost-effective, readily available, and easy to implement with minimal side effects and impact on workload of staff. Traditionally, post-operative analgesia has been provided by opioid analgesic [13,14]. Currently, a multimodal pain relief approach is currently being advocated as against the use of single agents [9,15].

Diclofenac is a non-steroidal anti-inflammatory drug of the phenyl acetic acid derivative [44-46]. It is a non-selective cyclooxygenase inhibitor (COX) [44-46]. It has half-life of 1.1hours [44-46]. It is well absorbed and food does not substantially change its bioavailability. It is metabolized in the liver by CYP2C9 and CYP3A4 [44-46]. Urinary excretion of unchanged diclofenac is less than 1%. Diclofenac can be administered via various routes including intramuscular, rectal and oral [45]. It can be used in combination with another forms of analgesia providing additive or synergistic effects, hence offering improved postoperative pain control [43,44].

Tramadol is a weak opioid which is an opioid mu1 receptor agonist [47] that acts by binding to opioid receptors and also by inhibiting the reuptake of serotonin and noradrenaline. It is metabolized into O-desmethyltramadol which is a more potent opioid [47,48]. It has more potency when combined with NSAIDs or non-opioids analgesics. It can be administered orally, parenterally and rectally. It is rapidly distributed in the body, and its plasma binding is about 20%. It is almost completely absorbed after oral (greater than 90%), rectal and intramuscular administration [46,47]. Its average bioavailability is 70% irrespective of current food intake, additionally; peak plasma concentration after oral, rectal and intramuscular administration is reached in 1-2 hours, 3 hours and 45 minutes respectively [48]. It has a half-life of 6 hours, onset of action <1 hour and duration of action was 4-6 hours and mainly excreted via the kidneys [44,46,48]. The maximum permissible dose is 400mg in 24 hours.

Acetaminophen is widely used for its analgesic and antipyretic actions but lacks anti-inflammatory properties [44,49]. It has activities related to NSAIDs and resembles especially the COX-2 selective inhibitors. It has weaker analgesic effect than NSAIDs or COX-2 selective inhibitors but has better tolerance. Despite this, its mechanism of action remained uncertain. Acetaminophen appears to have COX-2 selectivity and this is shown by its poor anti-platelet activity and good gastrointestinal tolerance. It has both central and peripheral effects [49,50]. It has bioavailability of 100% when given intravenously compared to 79% when given orally [51]. It's metabolized by the liver by glucuronidation and sulphation to non-toxic conjugates.

Currently, there is no gold standard for post-Caesarean pain management [16,17]. There are various options used in post-caesarean pain management but the choices depend on the availability of the drug, efficacy, side effect profile, cost, hospital protocols, individual preferences and financial disposition [12]. Various analgesics have been used for pain management after caesarean section whether singly or in combination. The analgesics include opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetics, these can be administered via systemic or neuroaxial route [18-20]. Because multimodal analgesics have different mechanism of actions, they can have synergistic or additive effects [20]. In our center, there is no exert protocol and no study has been done to compare the effectiveness of diclofenac-tramadol with diclofenac-acetaminophen combinations for post-Caesarean pain control. This study will compare both groups and will suggest a better pain relief in post-Caesarean patients. It may also give birth to our Centre protocol. Hence, the aim to undertake this study.

Methodology

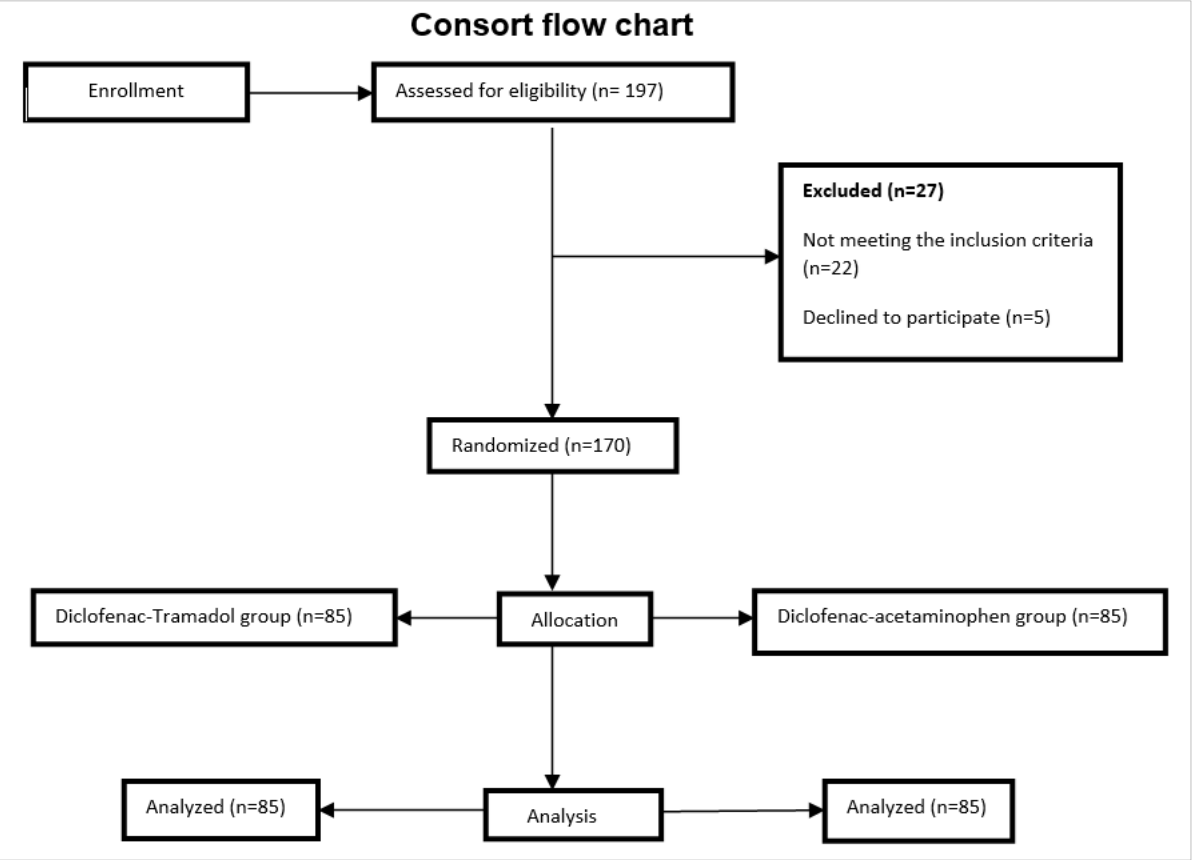
This was a clinical equivalence double-blinded randomized controlled trial on the effectiveness of diclofenac-tramadol and diclofenac-acetaminophen for pain relief within 24 hours of caesarean section at Alex Ekwueme Federal University Teaching Hospital, Abakaliki. The study lasted for a period of six months from February 10, 2021 to August 12, 2022. A total of 170 women who had both elective and emergency cesarean section within the study period and met the inclusion criteria and consented to the study were recruited. Randomization was done using a computer-generated random numbers with the aid of the software Research Randomiser. Patients were recruited into the appropriate arms. Group A received intramuscular 100mg of Tramadol 8 hourly after Caesarean section for 24 hours. Group B received intramuscular 600mg of acetaminophen by 8 hourly after Caesarean section for 24 hours. All participants received intramuscular diclofenac 75mg 8hourly for pain relief and intramuscular metoclopramide 10mg as a prophylactic antiemetic. The pain control was assessed using visual analogue scale while patients' satisfaction was assessed with Likert scale.

The primary outcome measures were the postoperative pain score at rest and movement within the first 24 hours. While the secondary outcome Measures were maternal side effects within the first 24 hours and maternal satisfaction at the end of 24-hour period

Data Collection and Analysis

All data sheets were collected at the end of the study. The sheets were separated using the record of randomization sequence. Their data were recorded in the appropriate groups. The generated data were analysed with IBM-SPSS software version 22(Chicago II, USA) 2015. Absolute and relative frequencies and percentages of categorical variables; mean, range and standard deviation of continuous variables were calculated. Independent student's-test was used for comparison between groups of continuous variables while chi-square ($\chi 2$) test (or Fisher's exact test where applicable) was used for categorical variables. P-value of <0.05 was taken as significant.

Result



Over the study period, a total of 170 participants who met the inclusion criteria were recruited into the study. The subjects were distributed 85 for each group.

Table 1: Socio-demographic and obstetric variables of the participants

Variables	Group A Tramadol (n=85)	Group B Acetaminophen group (n=85)	$\chi 2$	P-value
Age (years)				
<20	6 (7.1%)	7 (82%)	4.088	0.130
20-34	48(56.5%)	59(69.4%)		
≥35	31(36.5%)	19(22.4%)		
Marital status				
Married	69(81.2%)	76(89.4%)	2.298	0.130
Single	16(18.8%)	9 (10.6%)		
Highest level of education				
Primary	6 (7.1%)	9 (10.6%)	0.773	0.697
Secondary	54(63.5%)	50(58.8%)		
Tertiary	25(29.4%)	26(30.6%)		
Tribe				
Igbo	65(84.4%)	70(83.3%)	2.653*	0.466
Yoruba	2 (2.6%)	6 (7.1%)		
Hausa	4 (5.2%)	2 (2.4%)		
Others	6 (7.8%)	6 (7.1%)		
Parity				
0	14(16.5%)	10(11.8%)	1.576	0.455
1-4	61(71.8%)	68(80.0%)		
≥5	10(11.8%)	7 (8.2%)		
Booking status				
Booked	61(71.8%)	56(65.9%)	0.685	0.408
Unbooked	24(28.2%)	29(34.1%)		
Previous scar				
Yes	14(16.5%)	23(27.1%)	2.798	0.094
No	71(83.5%)	62(72.9%)		

Table 1 above shows the socio-demographic characteristics of participants. This showed no significant difference in any of the parameters between the two study groups. Thus the participants in this study were similar in the above characteristics.

Table 2: Postoperative pain scores at rest (using VAS) between the groups

Variables	Group A Tramadol (n=85)	Group B Acetaminophen (n=85)	t-test	P-value
1st hour VAS	3.01±1.15	3.94±0.78	6.176	<0.001*
6th hour VAS	2.51±1.23	2.82±0.68	2.086	0.039*
12th hour VAS	2.16±0.84	2.60±0.58	3.919	<0.001*
18th hour VAS	1.80±0.77	2.33±0.57	5.119	<0.001*
24th hour VAS	1.28±0.50	1.91±0.68	6.775	<0.001*
Composite scores**	2.15±0.72	2.72±0.38	6.441	<0.001*

**Statistically significant ** 24 hours average scores VAS- visual analogue scale*

As seen on table 2, the mean pain scores using the visual analog scale in the first 24 hours assessed at the 1st, 6th, 12th, 18th and 24th hour were higher in the Acetaminophen group compared to Tramadol group. The difference was statistically significant. The mean pain scores in both groups continued to improve with time but the tramadol group maintained the comparative advantage of better analgesia.

Table 3: Postoperative pain scores with movement (using VAS) between the groups

Variables	Group A Tramadol (n=85)	Group B Acetaminophen (n=85)	t-test	P-value
1st hour VAS	3.31±1.08	4.07±0.77	5.318	<0.001*
6th hour VAS	2.95±0.83	3.40±0.79	3.598	<0.001*
12th hour VAS	2.71±0.77	2.96±0.52	2.568	0.011*
18th hour VAS	2.26±0.73	2.74±0.44	5.235	<0.001*
24th hour VAS	1.71±0.77	2.38±0.53	6.605	<0.001*
Composite scores**	2.59±0.70	3.11±0.35	6.190	<0.001*

**Statistically significant ** 24 hours average scores VAS- visual analogue scale*

As shown on table 3, the mean pain scores using the visual analog scale in the first 24 hours assessed at the 1st, 6th, 12th, 18th and 24th hour were higher in the Acetaminophen group compared to Tramadol group. The mean pain scores in both groups continued to improve with time but the Tramadol group maintained the comparative advantage of better analgesia.

Table 4: Maternal satisfaction on the postoperative analgesia

Variables	Group A Tramadol (n=85)	Group B Acetaminophen (n=85)	χ2	P-value
Very satisfied	57(67.1%)	26(30.6%)	27.777*	<0.001
Satisfied	24(28.2%)	47(55.3%)		
Neither satisfied/dissatisfied	2 (2.4%)	10(11.8%)		
Dissatisfied	2 (2.4%)	0 (0.0%)		
Very dissatisfied	0 (0.0%)	2 (2.4%)		

** Fisher's exact test used*

Table 4 shows the maternal satisfaction of the participants with postoperative analgesia. Participants in the Tramadol group were more satisfied than those in the acetaminophen group and the difference was statistically significant.

Table 5: Side effect profile of the study participants

Variables	Group A Tramadol (n=85)	Group B Acetaminophen (n=85)	χ2	P-value
No side effect	69(81.2%)	78(91.8%)	5.0637*	0.084
Drowsiness	9 (10.6%)	4 (4.7%)		
Nausea	6 (7.1%)	2 (2.4%)		
Epigastirc pain	1 (1.2%)	1 (1.2%)		
Vomiting	0 (0.0%)	0 (0.0%)		

** Fisher's exact test used*

Table 5 above shows side effect profile of the participants. Majority of the participants had no side effects. More participants among those who received Tramadol had drowsiness as compared with those in Acetaminophen group. This was also similar for those who had nausea. However, the difference was not statistically significant.

Table 6: Need for rescue analgesia

Need for Rescue Analgesia	Group A Tramadol (n=85)	Group B Acetaminophen (n=85)	χ2	P-value
Yes	29(34.1%)	54(63.5%)	14.714	<0.001
No	56(65.9%)	31(36.5%)		

Table 6 shows the need for rescue analgesia. There was an increase need for rescue analgesia to control pain in the Acetaminophen group compared to Tramadol group and this was statistically significant.

Table 7: Level of association between type of caesarean section and pain score at rest and on movement

Variables	Elective	Emergency	t-test	P-value
	(n=24)	(n=61)		
Acetaminophen at rest				
1st hour VAS	3.92±0.78	3.95±0.78	0.181	0.857
6th hour VAS	3.04±0.69	2.74±0.66	1.895	0.062
12th hour VAS	2.75±0.61	2.54±0.57	1.503	0.137

18th hour VAS	2.50±0.51	2.26±0.58	1.769	0.081
24th hour VAS	2.00±0.59	1.87±0.72	0.795	0.429
Composite scores**	2.84±0.37	2.67±0.37	1.902	0.061
Acetaminophen on movement				
1st hour VAS	3.96±0.91	4.11±0.71	0.844	0.401
6th hour VAS	3.33±0.87	3.43±0.76	0.486	0.628
12th hour VAS	2.96±0.46	2.97±0.55	0.070	0.944
18th hour VAS	2.92±0.28	2.77±0.47	0.149	0.148
24th hour VAS	2.42±0.50	2.36±0.55	0.433	0.666
Composite scores**	3.12±0.39	3.11±0.34	0.099	0.921
	(n=30)	**(n=55)**		
Tramadol at rest				
1st hour VAS	3.33±1.56	2.84±1.12	1.936	0.056
6th hour VAS	2.40±1.04	2.56±1.33	0.583	0.561
12th hour VAS	2.13±0.73	2.18±0.91	0.252	0.802
18th hour VAS	1.87±0.73	1.76±0.79	0.588	0.558
24th hour VAS	1.33±0.61	1.25±0.44	0.688	0.493
Composite scores**	2.21±0.70	2.12±0.73	0.569	0.571
Tramadol on movement				
1st hour VAS	3.53±1.22	3.18±0.98	1.443	0.153
6th hour VAS	3.03±0.85	2.91±0.82	0.658	0.513
12th hour VAS	2.73±0.69	2.69±0.81	0.242	0.810
18th hour VAS	2.13±0.63	2.33±0.77	1.179	0.242
24th hour VAS	1.87±0.82	1.62±0.73	1.433	0.156
Composite scores**	2.66±0.73	2.55±0.68	0.722	0.473

*** 24 hours average scores*

Table 8 shows the level of association between the type of caesarean section and the postoperative pain score at rest and with movement in both study groups. The type of caesarean section had no significant effect on the pain scores at rest and with movement.

Discussion

Post caesarean section pain relief is essential for reducing post-operative stress, and this provides subjective comfort and facilitating postoperative recovery. This study compared the post caesarean analgesic effect between diclofenac-tramadol and diclofenac-acetaminophen combinations. In this study, the maternal socio-demographic characteristics were similar and comparable between the two groups. This showed that that the socio-demographic variables were evenly distributed between the two groups and this eliminated any possible confounding influence from them. This was similar to reviewed studies with similar drug combination [20,22,51,52].

This study found that both diclofenac–acetaminophen and diclofenac–tramadol combinations effectively controlled pain. This was in line with study by Mitra et al [22] that showed that both combinations can achieve satisfactory post-operative pain control. However, Tramadol group maintained the comparative advantage of better analgesia and this explained the use of rescue analgesia in acetaminophen group. This was also demonstrated by Mitra et al [22] were they noted that the diclofenac–tramadol combination was overall more efficacious than diclofenac-acetaminophen but associated with higher incidence of post-operative nausea. This study result differ from the study by Adeniji et al [20], they reported that the Pentaxocin-Peroxicam (PP) group had better pain control than the Tramadol-Pentazocine (TP). This may be because of their different mechanism of action as TP are both opioid and acts on the opioid receptor whereas PP acts on both opioid receptor and NSAIDS pathway.

Maternal satisfaction has been described as an imprecise measure of assessing the effectiveness of post-operative pain management. Diclofenac and Tramadol combination showed better maternal satisfaction compared to the diclofenac and acetaminophen combination. It could be that the sedative effect of Tramadol contributed to the level of satisfaction. This is similar to study by Adeniji et al [20] who noted that the use of PP or TP had better satisfaction that pentazocin or tramadol alone. Also, both Kwosah et al [52] and Egede et al [51] recorded good maternal satisfaction when bimodal agents were used compared to unimodal agent as was seen in our study were we used bimodal agents, though both unimodal agents and pentazocine were not considered in our study. However, Mitra et al [22] did not study the level of maternal satisfaction and this was one of the gaps noted justifying the reason for our study.

In comparing the side effect profile, nausea and drowsiness was commonest. However, the diclofenac-acetaminophen combination was associated with fewer side effects. Compared to study by Mitra et al [22], they had lesser side effect of nausea. This could be that the antiemetic they used ondansentron, is known to be more potent that metoclopramide used in our study. When compared with studies by Kwosah et al [52] and Egede et al [51], there were higher side effect of dizziness. This maybe the presence of pentazocine used in these studies unlike ours. The mean pain score association between the type of caesarean section and mean pain score at rest and with movement between both groups was similar. Kwosah et al [52], Egede et al [51] and Mitra et al [22] did not compare using the type of caesarean section. This was another area of knowledge gap noted which this study answered.

Conclusion

Both diclofenac-tramadol and diclofenac–acetaminophen combinations effectively controlled pain in women that underwent caesarean section within the first 24 hours. The diclofenac-tramadol combination was significantly more effective for pain control and associated with increased participants' satisfaction with minimal side effects. The implication is that diclofenac–tramadol combination can be used in cases where Tramadol is considered safe, however, in any circumstance where Tramadol (or any opioid) use is considered unsafe or risky, injectable acetaminophen can be used as acceptable safe alternative to Tramadol in combination with diclofenac. Thus, the results of this study expand our therapeutic options and further empower the clinician in the management of this important group of patients.

Recommendation

1. Diclofenac-tramadol should be used in preference to diclofenac-acetaminophen for post-caesarean pain relief after a multicenter trial has noted similar result.
2. The use of tramadol and diclofenac for immediate post caesarean section pain relief may be considered as part of departmental protocol in Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital Abakaliki.
3. A multi-centered study with similar design and drugs of study like these ones will be necessary to substantiate the outcome of this study.

Informed Consent

A signed consent was obtained by the researcher and research assistants before recruitment of the participants into the study after appropriate counselling.

Ethical Considerations

Ethical clearance was obtained from the Hospital and Research Committee (HREC) of the Alex Ekwueme Federal University Teaching Hospital and Mile Four Hospital, Abakaliki. Patients signed written and informed consent form after careful explanation of the objectives, procedure and full implication of participation in the study. This study was conducted in compliance with the ethical standards of our institution on human subjects as well as with the Helsinki Declaration.

Conflict Of Interest

There was no conflict of interest.

Funding

The entire financial burdens were burn by the researchers.

Author Contributions

Paschal Chijioke OKOYE: The principal investigator
Chidebe Christian ANIKWE and Arinze C IKEOTUONYE: Supervised the work.
Darlington-Peter Chibuzor UGOJI, Emmanuel Chijioke UWAKWE, Njideka Linda OKOYE and Ikenna Chidi EBERE: were involved in the literature search and day to day conduct of the work till conclusion.

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Data Availability

Data would be available upon reasonable request.

List of Abbreviations

Mg: Milligram
X2: Chisquare
<: Lessthan
%: Percentage
Vs: Verses
COX: Cyclooxygenase
CYP2C9: Cytochrome P2CP
CYP3A4: Cytochrome 3A4
NSAID: Non-steroidal anti-inflammatory drugs
SPSS: Statistical package for social science
VAS: Visual analogue scale
N: Number
PP: Pentazocine Peroxicam
TP: Tramadol Pentaxocine
HREC: Hospital and Research Committee

References

[1] Otubu JA. Caesarean section in Agboola (ed) Textbook of Obstetrics and Gynaecology for medical students. Heinemann Eductional Books (pubs) 2006. 495-503.
[2] Betran AP, Je J, Moller A, Zang J, Gulmezoglu AM, Torioni MR. The increasing trend in Caessarean section rates: Global, regional and national estimates: 1990-2014. PLoS one. 2016; 11 (2): e0148343.
[3] Swende TZ, Agida ET, Jogo AA. Elective Caesarean section at the Federal Medical Centre Makurdi, North Central Nigeria: Nig J Med. 2007; 16(4): 372-374.
[4] Arulkumaran S. Malpresentation, Malposition; CPD and Obstetrics procedures. In Dewhurst's Textbook of Obstetrics and Gynaecology (ed Edmonds Dk) 8th ed. Wiley- Blackwell publishing ltd United Kingdom. 2012; 311-325.
[5] Eleje GU, Udigwe GO, Akabuike JC, Eke AC, Eke NO, Umeobika JC. The rate of Caesarean section in Nnewi, Nigeria: A 10-year review. Afri Med J. 2010; 1(1): 11-14.
[6] Bethran AP, Torloni MR, Zhang J, Gulmezoglu AM. WHO working group of caesarean section. WHO statement on caesarean section rate and summary. BJOG. 2016; 125 (5): 667-670.
[7] Onoh RC, Eze JN, Ezeonu PO, Lawani LO, Iyoke CA, Nkwo PO. A 10-year appraisal of Caesarean delivery and the associated fetal and maternal outcomes at a teaching hospital in Southeast Nigeria. Int J Womens Health.2015; 7: 531-538.
[8] Obuna JA, Ugboma HAA, Ejikeme BN, Umeora OUJ, Agwu UM. Pattern and outcome of higher order Caesarean section in a secondary health facility in Nigeria. Obstet Gynaecol. 2012; 1(3): 19-22.
[9] Ismail S. Multimodal analgesia for Caesrean section: Evolving role of transversus abdominis plane block. J Obstet Anaesth Crit care. 2012; 2: 67-68.
[10] Luana B, Olivia AC, Mark PO, George GB, Anthony SI, Maurice ZA et al. Predictors of post-Caesarean section pain and analgesic consumption. J Anaesthesiol Clin Pharmacol. 2011; 27(2): 185-191.
[11] Vijayan R. Mnaging acute pain in the developing world. Pain.2011; 19(3): 1-7.
[12] Kuczkowski KM. Post-Caesarean analgesia: Quo Vadis? Anestezjologia ratownictwo. 2010; 4: 296-303.
[13] Pan PH. Post-Caesarean delivery pain management. Multimodal approach. Int J Obstet Anaesth. 2006; 15(3): 185-188.
[14] White PF. The role of non-opioid analgesic techniques in the management of pain ambulatory surgery. Anesth Analg. 2002; 94:577-85.
[15] Snell P, Hicks C. An exploratory study in the UK of the effectiveness of three different pain management regimens for post-Caesarean section women. Midwifery. 2006; 22(3): 249-61.
[16] Pickering E, Holdoroft A. Pain relief after Caesarean section. In: Kinsella M. Raising the standard; a compendium of audit Recipes. 2nd ed. London: Royal College of Anaesthetist; 206:168-9.
[17] Ismail S, Shahzad K, Shafia F. Observational Study to assess the effectiveness of post-operative pain of patient undergoing elective caesarean section. J Anaesthesiol Clin Pharmacol. 2012; 28: 36-40.

[18] Akhavanakbari G, Entezariasis M, Isazadehfar K, Khnamouiagdam F. The effects of indomethacin, diclofenac, and acetaminophen suppository on pain and opioids consumption after Caesarean section. Perspect Clin Res. 2013; 4 (2): 136-141.
[19] Shahraki AD, Jabalameli M, Ghaedi S. Pain relief after Caesarean section: oral methadone versus intramuscular pethidine. J Res Med Sci. 2012; 17 (2): 143-147.
[20] Adeniji AO, Atanda OOA. Randomized comparison of effectiveness of unimodal opioid analgesia with multimodal analgesia in post-Caesarean section pain management. J pain Res. 2013; 6: 1-6.
[21] Trivedi VA. Comparative clinical study of tramadol versus pentazocine for sedation and analgesia as premedication (A study of 60 cases). Int J Anesthesiol. 2009; 26 (1):
[22] Mitra S, Khandelwal P, Sehgal A. Diclofenac-tramadol versus diclofenac- acetaminophen combination for pain relief after Caesarean section. Acta Anaesth Scandinavia. ; 56 (6): 706-711.
[23] Stein C, Clark JD, Oh U. Peripheral mechanism of pain and analgesia. Brain Res Rev. 2009; 60 (1): 90-113.
[24] Cervero F, Laird JMA. Visceral pain. Lancet. 1999; 353: 2145-2148.
[25] Woolf CJ, Ma Q. Nociceptors- noxious stimulus detector. Neuron 2007; 55 (3): 353-364.
[26] Schafer M, Sorkin L. Effects of cytokines on neuronal excitability. Neurosci Lett. 2008; 437 (3): 188-193.
[27] White FA, Wilson NM. Chemokines as pain mediators and modulators. Curr Opin Anaesthesiol. 2008; 21 (5): 580-585.
[28] Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RSR. Clinical aspects of acute postoperative pain management and its assessment. J Adv Pharm Techn Res. 2010; 1 (2): 97-108.
[29] Mahama F, Ninnoni JPK. Assessment and management of postoperative pain among nurses at resource- constraint teaching hospital in Ghana. Nursing Res Pract. 2019. https://doi.org/10.1155/2019/9091467.
[30] Wood S. Postoperative pain 2: Patient education, assessment and management. Nursing Times. 2010; 106: 46.
[31] Myles PS, Myles DB, Galagher W, Boyd D, Chew C, MacDonald N. Measuring acute postoperative painusing visual analog scale: the minimal clinically important difference and patient acceptable symptom state. British J Anaesth. 2017; 118(3): 424-9.
[32] Elvir- Lazoa OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anaesthesiol. 2010; 23: 697-703.
[33] Vickers A. The management of acute pain. Surgery. 2010; 28 (4): 175-180.
[34] Vickers A, Bali S, Baxter A, Bruce G, England J, Heafield, R et al. Consensus statement on the anticipation and prevention of acute postoperative pain: multi-disciplinary RADAR approach. Curr Med Res Opinion. 2009; 25 (10): 2557-2569.
[35] Mackintosh C. Assessment and management of patients with postoperative pain. Nursing Standard. 2007; 5: 49-55.
[36] Hawker GA, Mian S, Kedzerska T, Frech M. Measures of adult pain; visual analogue scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short form pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). Arthritis Care Res. 2011; 63 (S11): S240- S250.
[37] Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K et al. Visual analogue scales (VAS): measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care. Allergo J Int. 2017; 26(1): 16-24.
[38] Hasson D, Arnetz BB. Validation and findings comparing VAS vs. Likert scale for psychosocial measurements. Int Electronic J health Edu. 2005; 8: 178-192.
[39] Pearse N. Deciding on the scale granularity of response categories of Likert type scale: The case of a 21- point scale. Electronic J Business Res Methods. 2011; 9(2): 159-171.
[40] Lim Y, Jha S, Sia AT, Rawal N. Morphine for post-Caesarean section analgesia: intrathecal, epidural or intravenous? Singapore Med J. 2005; 46 (8): 392.
[41] Kerai S, Saxena KN, Taneja B. Post-Caesarean analgesia: What is new? Indian J Anaesth. 2017; 61 (3): 200-214.
[42] Kivok S, Wong H, Sng BL. Post-Caesarean analgesia. Trends Anaeth Critical care. 2014; 4 (6): 189-194.
[43] Mcdonnell NJ. Analgesia after Caesarean delivery. Anaesth Intensive Care. 2009; 37: 539-551.
[44] Daniel EF, Robert Wu,Shraddha P. NonSteroidal Anti-inflammatory Drugs, disease-modifying antirheumatic drugs, non-opioid analgesics and drugs used in gout, In: Betranm G. Katzung (eds.) Basic & Clinical Pharmacology 12th edition, United States: McGraw-Hill Companies; 2012. p. 635-657.
[45] Tang W. The metabolism of diclofenac- enzymology and toxicology perspectives. Curr Metab. 2003; 4 (4): 319-329.
[46] Malek J, Sevcik P, Bejsovec D, Gabrhelik T, Hnilicova M, Krikava I et al. Postoperative pain management, 3rd ed. Czech Republic. Mlada Fronta; 2017.
[47] Papini JZB, Cereda CMS, Junior SAC, Ribeiro de Araujo, Tofoli GR. Pharmacokinetics and pharmacodynamics evaluation of tramadol in thermoreversible gels. Biomed Res Intern. 2017: 7 pages. Article Id 5954629. https:// doi.org/10.1155/2017/5954629.
[48] World Health Organization. Tramadol update review report. Agenda item 6.1. Expert Committee on drug dependence 36th meeting, Geneva, 16-20 June. 2014.
[49] Graham GG, Davis MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflamm Pharmo. 2013; 21(3): 201-232.
[50] Sharma CV, Mehta V. Paracetamol: Mechanisms and updates. Continuing Edu Anaesth Critical Care Pain. 2014; 14 (4): 153-158.
[51] Egede JO, Ajah LO, Umeora OU, Ozumba BC, Onoh RC, Obuna JA et al. Pentazocine alone versus pentazocine plus diclofenac for pain relief in the first 24 hours afterCaesarean section: A randomized controlled study. J Clin Diagnostic Res. 2017; 11 (4): QC 01- QC 05.
[52] Kwosah NJ, Awoyesuku PA, MacPepple DA, John DH. Comparative effects of single agent rectal diclofenac versus a combination of rectal diclofenac and intramuscular pentazocine, on post Caesarean section pain relief in a tertiary institution in Southern Nigeria. J Adv Medicine Med Res. 2019; 31 (2): 1-10.
[53] Zhong B. How to calculate sample size in Randomized Controlled Trial? J of Thoracic Dis 2009; 1(1): 51-54.