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Clinical Study

The Use of Lidocaine and Bupivacaine Mix in Adult Safe Male Circumcision: Less Is More

M. Galukande,[1,2] S. Hodges,[3] K. Duffy,[4] A. Coutinho,[5] and S. Kaggwa[2]

[1]*International Hospital Kampala, Surgery Department, Mulago Hospital, Kampala, Uganda*
[2]*Department of Surgery, College of Health Sciences, Makerere University, Kampala, Uganda*
[3]*International Hospital Kampala, Kampala, Uganda*
[4]*International Medical Group, Kampala, Uganda*
[5]*Infectious Diseases Institute, Makerere University, Kampala, Uganda*

Correspondence should be addressed to M. Galukande; mosesg@img.co.ug

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Introduction. Lignocaine is (with or without bupivacaine) the only drug recommended for local anesthesia for safe adult male circumcision (SMC). This study evaluated the effectiveness of postoperative pain control when using two different concentrations. *Methods*. An observational analytical study conducted at an urban high volume site. Pain was assessed using the Visual Analogue Scale. Mixtures of lignocaine 2%, bupivacaine 0.5% (LiB), and water in ratios of 4 : 4 : 2 and 3 : 3 : 4 were compared. *Results*. Data from 217 clients were analyzed: 100 in the 4 : 4 : 2 group and 117 in the 3 : 3 : 4 group. Clients in the 4 : 4 : 2 group had more pain, at 60 minutes, compared to the 3 : 3 : 4 group ($p = 0.035$). The 3 : 3 : 4 mix used 70% less lignocaine and 90% less bupivacaine (60 mg and 15 mg); the allowable maximum dosages are 200 mg and 150 mg, respectively. *Conclusion*. The 3 : 3 : 4 mix was superior to the 4 : 4 : 2 mix. This has implications for supply chain management and potential reduction of LA toxicity. We therefore recommend the 3 : 3 : 4 mix for routine adult SMC.

1. Introduction

Lidocaine, also known as lignocaine, is one of the most widely used local anesthetic agents in surgical practice and it is recommended (with or without bupivacaine) for safe adult male circumcision (SMC) for partial HIV prevention in 14 sub-Saharan countries [1]. Male circumcision (MC) has been shown to reduce the risk of HIV [2–5] and HIV prevention programs in sub-Saharan Africa have initiated SMC implementation.

Since 1947, lignocaine has been used safely and effectively for almost every possible type of procedure requiring local anesthetic [6]. It has a rapid onset of action and is effective for 30–60 minutes in its plain form (or up to 90 minutes when used with a vasoconstrictor), and when combined with bupivacaine pain control, it lasts several hours. Local anesthetics are not free of complications [7] and the risk of systemic toxicity is a concern for many SMC clinicians and program managers.

Lignocaine is a tertiary amine that is an amide derivative of dimethylaminoacetic acid. Allergic reactions to the amide group of local anesthetic are extremely rare and the vast majority of adverse reactions result from systemic toxicity [8]. The maximum dose of plain lignocaine is the subject of debate. The manufacturers recommend 200 mg in the adult; however, some clinicians often use up to 500 mg or more depending on the procedure being performed. Whilst using the infiltrative technique of injecting lignocaine, 500 mg is a safe maximum for plain lignocaine (670 mg with lidocaine plus adrenaline); these higher dosages are recommended only for dilute solutions such as 0.4% and 0.5% lignocaine. The 0.2% solution can permit the use of even higher dosages [9]. Bupivacaine, introduced in 1963, is the butyl derivative of N-alkyl pipecoloxylidine. Though it gained much popularity owing to its longer duration [10], there are however systemic toxicity concerns [11].

The objective of this study, therefore, was to assess self-reported pain and adverse events when using two different

concentrations of lignocaine and the bupivacaine mixture while performing routine SMC.

2. Methods

2.1. Design. This was an observational analytical study.

2.2. Setting. The study is conducted at an urban high volume SMC site in a resource limited setting, over a 6-week period in 2013.

2.3. Participants. Adult males aged 18–49 years presenting for routine voluntary SMC were recruited for enrollment. All men were offered voluntary HIV counseling and testing before the surgery, received group counseling/health education on HIV prevention, and were offered HIV testing, individual counseling was necessary to address questions and to clarify any queries, and free condoms were available. All participants were screened for contraindications to SMC such as active sexual transmitted infections (STI), commonly manifesting as urethral discharge or penile ulcers.

2.4. Ethical Consideration. All participants after they were counseled provided written informed consent. Ethical approval was obtained from the Makerere College of Health Sciences Ethics and Research Committee.

2.5. Lidocaine and Bupivacaine (LiB) Mixtures and Procedure. Lidocaine 2% and bupivacaine 0.5% were procured locally, from suppliers licensed and approved by the national drug authority (NDA), and were within the expiry date. The 4 : 4 : 2 mix was 4 cc of lignocaine 2%, 4 cc of 0.5% bupivacaine, and 2 cc of water for injection, all drawn into a 10 cc syringe. The 3 : 3 : 4 mix was 3 cc of lignocaine 2%, 3 cc of bupivacaine 0.5%, and 4 cc of water for injection.

We assigned participants to the two groups (each group on alternative weeks). We administered additional local analgesia for those who experienced breakthrough pain during the procedure. We recorded the mix ratio, the time the procedure commenced and ended using a stop clock, presence of breakthrough pain during SMC, and pain at 30 and 60 minutes after SMC (postoperative). The assessor for pain was blinded to the LA dosing ratio. We encouraged clients to report pain and a visual analogue score (VAS) pain chart was used to estimate pain intensity. Postoperative pain was graded as mild if the VAS scores were 0–5, moderate if scores were 6–8, and severe if scores were 9-10. We monitored the clients in the recovery room for additional postoperative pain and oral analgesia was given when and if needed.

Regarding other adverse events, participants were observed for CNS (central nervous system) toxicity, convulsions, coma, respiratory depression, and CVS toxicity bradycardia PR <60 bpm (beats per minute).

2.6. Data Analysis. Data were collected using a questionnaire, we used SPSS v 16 for the analysis, descriptive statistics were run, and comparison of means using chi-square and the independent t-test and significance was considered when the p value was less than 0.05.

Table 1: Showing the characteristics of clients who underwent SMC.

Variable	Value
Age $n = 217$	
Mean	25 years
SD	7
Weight $n = 185$[†]	
Mean	62.3 kg
SD	10.8
Type of cadre $n = 214$	
Nurse	205
Clinical officer	2
Doctor	7
Missing	3
MC method used $n = 216$	
Sleeve resection	216
Dorsal slit	0
Forceps guided	0
Anesthesia mix $n = 217$	
Mixed bupivacaine and lignocaine	217
Anesthesia application	
Two ring blocks	216
Penile block	1
Ratio used	
4 : 4 : 2	100
3 : 3 : 4	117
Quantity used	
10 cc	217

[†]Missing = 32.

3. Results

In total, 217 clients were included in the study: 100 in the 4 : 4 : 2 group and 117 in the 3 : 3 : 4 group; all received a mixture of LiB and water for injection in the ratios indicated. Table 1 shows the characteristics of these clients; the mean age was 25 years and the procedures were mostly performed by nurses under the supervision of doctors. We used the sleeve resection method predominately and in all but one a penile ring block infiltration was used to administer local anesthesia.

Differences in pain control were observed 60 minutes after the SMC procedure, and clients in the 4 : 4 : 2 groups had higher pain scores than the 3 : 3 : 4 group ($p = 0.035$) as shown in Table 2. There were no occurrences of LiB toxicity events during this study. There was no observed manifestation of CNS or CVS over toxicity.

4. Discussion

We set out to assess the effectiveness of two LiB mixtures in the control of pain during and after SMC. We have found that the 3 : 3 : 4 LiB mix used less of each local

Table 2: Comparing the means of the two groups, 4 : 4 : 2 and 3 : 3 : 4.

Variable	4 : 4 : 2 group $n = 100$	3 : 3 : 4 group $n = 117$	p value
Age	26 years	25 years	0.280
Weight	63 kg	61 kg	0.900
Breakthrough pain (during procedure)	2	8	0.079
Those with pain at zero minutes (just after procedure)	3	1	0.083
Those with pain at 30 min (after procedure)	20 (20%)	28 (26%)	0.351
Those with pain at 60 min (after procedure)	35 (38%)	26 (24%)	0.035
Mean pain score at zero	5 (3–8)	2	0.370
Mean pain scores at 30 min	4 (1–9)	3.4 (1–9)	0.209
Mean pain score at 60 min	3.3 (1–8)	3.5 (1–7)	0.695
LiB related AEs reported	0	0	—

For the scores at 30 min: those who had a pain score below or equal to 5 (mild pain) were 11/20 and 25/28 for the 4 : 4 : 2 and 3 : 3 : 4 groups, respectively.
For the scores at 60 min: those who had a pain score equal to or below 5 (mild pain) were 23/35 and 19/26 for 4 : 4 : 2 and 3 : 3 : 4 groups, respectively.
Those who registered a pain score of 9 were 2 (<1%), one in each group; all clients that reported pain received additional oral analgesia, and they were not in distress.
All breakthrough pain (during procedure) was classified as mild.

anesthetic when compared to the current practice in Uganda. The currently recommended and commonly used LiB mix consists of 10 cc of 1% lignocaine (100 mg) and 10 cc of 0.25% (25 mg) bupivacaine [12]. The 3 : 3 : 4 LiB mix in this study used 40–70% less anesthetic than recommended by the manufacturers. It was effective in the control of pain during and immediately after SMC and would potentially save on the use of bupivacaine and lignocaine without compromising pain control. It reduces the potential risk of LA toxicity.

In this study approximately 7% of the men reported feeling some discomfort/mild pain intraoperatively, with pain scores equal to or less than 4. In a study in Rakai Uganda [12], the breakthrough rate for their LiB group was 1.7%, though the mix ratios were different and the volumes were twice as much as we used in this study. In a recent circumcision study in Scotland [13], 25% of the men felt mild pain (mean pain score 3.3) throughout the procedure and were given additional LA. In a paper by Vinckier [14], it is stated in general practice that 7% of those who receive local anesthesia will fail. Possible causes of failure are presence of infection prior to LA use, incorrect selection of local anesthetic solution, technical mistakes, and anatomical variations with accessory innervation and the anxiety of the client [15].

Some of the major challenges facing SMC program implementation in sub-Saharan Africa includes a reliable, cost effective, consistent supply of good quality supplies and drugs for the programs [16]. Whereas ensuring a steady supply of consumables would be one of the solutions to the problem, rational use is another one. Rational use of local anesthetics, from the point of view of both toxicity and cost, entails using the least, but most effective, mix and dosage [6, 9, 11].

The 3 : 3 : 4 LiB mix used in this study delivers only 30 mg of lignocaine and 7.5 mg of bupivacaine and 4 : 4 : 2 mix delivers 40 mg of lignocaine and 20 mg of bupivacaine. Some workers have recommended doses beyond 3 mg/kg, up to 7 mg/kg, if the infiltrative technique is used [9, 17–19].

Lignocaine toxicity has been reported after subcutaneous administration, oral administration, and intravascular injection [20–22] and therefore should be used cautiously.

The dosages we used in this study are much less than what is currently recommended in Uganda and below the recommended maximum dosage of 200 mg for lignocaine and 175 mg for bupivacaine, by manufacturers. Although there have been few reports of severe local anesthetic toxicity, in the advent of upscale of SMC, the likelihood of more cases is not a misplaced concern. Included in toxicity is transient neuropathy symptoms, seizures, arrhythmias, cardiac arrest, and death. Severe toxicity is very difficult to manage outside of higher level medical facilities with intensive care units [23, 24]. It is therefore prudent to consider using less to gain more in terms of safety and perhaps cost reduction.

Recently the cost of 10 cc 2% lignocaine and 10 cc 0.5% bupivacaine was estimated to be $3 per client [12]; the 3 : 3 : 4 mix cost would be $1 in Uganda (2013) and thus presents potential for some cost savings program.

5. Limitations

Use of the pain score chart may have posed interpretation challenges by some participants; however, most of the participants in this study had at least a secondary level of education and therefore familiar with such visual scales. There was no anxiety assessment prior to performing MC; higher anxiety levels could have influenced pain perception for those reporting pain, especially high scores leading to an overestimation of pain.

6. Conclusion

The 10 cc 3 : 3 : 4 (2% lignocaine, 0.5% bupivacaine, and water for injection) LiB mix was superior to the 4 : 4 : 2 mix and used less local anesthetic than currently used in SMC programs in Uganda. This potentially offers less risk of toxicity exposure

for adult men presenting for SMC. Other SMC programs in sub-Saharan Africa could consider exploring this option.

Abbreviations

MC: Male circumcision
LiB: Lignocaine and bupivacaine
SMC: Safe male circumcision
VMMC: Voluntary medical male circumcision
MC: Male circumcision.

Competing Interests

The authors declare no competing interests.

Authors' Contributions

M. Galukande originated the concept, analyzed the data, and wrote the first draft. S. Hodges, K. Duffy, S. Kaggwa, and A. Coutinho performed critical reviews for intellectual content.

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