Council Lecture

Comparison of Magnesium Sulfate Versus Hyaluronidase as Adjuvants in Peribulbar Anaesthesia for Cataract Surgery at National Eye Centre, Kaduna, North-West Nigeria

Abdulrazak MomohJimoh[1], Emmanuel O. Babalola[2], Mahmoud B. Alhassan[3], Aminatu A. Abdulrahman[3], Murtala M. Umar[3], Lukman A. Raji[3], Ugochukwu A. Eze[4]

[1]Department of Ophthalmology, Federal Medical Centre, Keffi, Nigeria;
[2]Department of Ophthalmology, Rachel Eye Centre, Abuja, Nigeria
[3]National Eye Centre, Kaduna, Nigeria
[4]Department of Ophthalmology, Federal Medical Centre, Asaba, Nigeria

Corresponding author: Dr. Abdulrazak MomohJimoh, Department of Ophthalmology, Federal Medical Centre, Keffi, Nigeria. *Email:* momohrazak95@gmail.com

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ABSTRACT

Background: Akinesia and analgesia are important for successful ophthalmic surgery. The efficacy of local anaesthesia can be enhanced by the use of adjuvants such as Hyaluronidase and Magnesium sulfate. Magnesium sulfate is readily available and has a long shelf life, while Hyaluronidase which is more commonly used has some associated drawbacks such as the risk of anaphylaxis, short shelf-life and not being readily available in some parts of Nigeria.

Aim: To compare the effects of Magnesium sulfate versus Hyaluronidase as adjuvants in Peribulbar anaesthesia for cataract surgery.

Methods: A randomized, controlled, double-blinded experimental study involving 150 patients with age-related cataract surgery was carried out between October and December 2020. They were randomly allocated into three groups of fifty (50) subjects each. All the patients received a peribulbar local anaesthetic (LA) injection. Magnesium sulfate group had an additional 80mg of $MgSO_4$ in 0.5mls of normal saline (N/S). Hyaluronidase group had an additional 15.0 IU of hyaluronidase while the control group had an addition of 0.5mls of plain normal saline. Ocular akinesia score, duration of globe akinesia, and postoperative pain score were assessed.

Result: There was an earlier onset and longer duration of akinesia among the magnesium sulfate group compared to other groups ($p < 0.001$). There was no significant difference in the postoperative pain scores across the groups ($p > 0.850$).

Conclusion: These findings suggest that there is better akinesia and prolonged duration of peribulbar block with adjuvant magnesium sulfate.

Key words: Cataract, Magnesium sulfate, hyaluronidase, peribulbar, anaesthesia,

INTRODUCTION

Local anaesthesia involves the blockage of a nerve serving a part of the body. It is the method of anaesthesia for many ophthalmic surgeries, especially in adults. The commonly employed techniques are retrobulbar, peribulbar, sub-Tenons, subconjunctival, topical and intracameral techniques.[1-3] Among regional blocks, peribulbar block provides efficient anaesthesia with low incidence of complications. However, it has a slow onset of action and frequent supplementation may be needed. Ophthalmic surgeons sometimes face challenges during surgery when there is inadequate analgesia and ocular akinesia. This may require extra-anaesthetic injection intra-

operatively with the attendant risk of injection and anaesthesia related complications. Inadequate akinesia can make surgery clumsy and difficult for the surgeon especially the trainee with less experience. This is quite common during rural surgery posting of ophthalmology residents in our setting.[4,5] Many additives have been used in peribulbar block to hasten the onset of akinesia, improve the quality and duration of anaesthesia, thereby reducing the required dose of anaesthetic agents with the eventual decrease in the incidence of side effects caused by the use of high-dose local anaesthetics. Examples of such additives are hyaluronidase, adrenaline, clonidine, corticosteroids, sodium bicarbonate, magnesium sulfate ($MgSO_4$), and neuromuscular blocking agents like rocuronium. Adequate akinesia of the eyelids and globe are highly desirable during surgery to achieve good exposure and prevent orbicularis muscle contraction that can result in elevated orbital and intraocular pressure leading to extrusion of ocular contents.[6]

Magnesium is one of the major ion constituents in human body fluid. It acts on N-Methyl–D–Aspartate receptor, causing blockage of calcium influx, hence muscle relaxation.[7] Magnesium acts as a calcium channel blocker at presynaptic nerve terminals and reduces acetylcholine release, which diminishes muscle fiber excitability; the amplitude of endplate potential, resulting in the potentiation of a neuromuscular blockade. [8, 9]

The need to study magnesium sulfate ($MgSO_4$) as an alternative agent that is cheaper, readily available, has a longer shelf life, and lower risk of side effects is expedient in resource poor settings like ours.

Hyaluronidase enhances the spread of local anaesthetic agents. It has its drawback in terms of the associated risk of anaphylaxis; short shelf-life; and availability.[10, 11]The purpose of this RCT was to compare the adjuvants effects of magnesium sulfate and hyaluronidase on peribulbar anaesthesia.

PATIENTS AND METHODS

The study was carried out at National Eye Centre, Kaduna, North-West Nigeria and involved 150 patients with age related cataract scheduled for small incision cataract extraction between October to December 2020.

The inclusion criteria were as follows: Patients with age-related cataract scheduled for elective manual small incision cataract surgery who consented for the study; Axial length (18-26mm); American society of anesthesiologists physical status (ASA) I and II.

Patients that were excluded from the study included those with ASA III and above, history of allergy to local anaesthetic agents, bleeding disorder, impaired mental status/Challenges with communication, previous ocular surgery in the same eye, ocular motility disorder/ocular muscle palsy, ocular trauma, , diabetes mellitus, complicated surgery that required prolonged stay on operating table or extra-surgical procedures and marked uncontrolled tremors.

Ethical consideration: Approval of Ethics and Research Committee of the National Eye Centre, Kaduna was sought before the study and Informed consent taken from the participants. The tenets of Helsinki declaration were adhered to.

Study Procedure:

This was a randomized, controlled, double-blinded experimental study. Sample size was calculated as that required to detect a difference of at least 1 eye with successful akinesia score between two main groups (effect size = 1); at an α error of 5%, a β error of 10% and assumption of variance of 2, and attrition rate of 10%. Using the formula for comparison of means[12], the estimated sample size was 50 subjects per group. Consented eligible patients with senile cataract, scheduled for elective small incision cataract surgery were recruited and those enrolled were randomly allotted into the three equal arms: A, B and C of magnesium sulfate; hyaluronidase; and control, respectively, by a balanced stratified randomization technique using a computer program to generate a sequence of random numbers for the $MgSO_4$, hyaluronidase and control groups respectively. The random sequence number was generated by an independent research assistant and was placed in a sealed, opaque envelope labeled A (containing $MgSO_4$); B (containing hyaluronidase); and C (containing control) depending on the group on the sequence number.

The 150 sealed envelopes were divided into 2 parts/strata as was generated from the computer random sequence number (for male

and female), making 75 subjects in each stratum. Each of the above parts (strata) were apportioned with 25 of 'A' ($MgSO_4$); 25 of 'B' (hyaluronidase); and 25 of 'C' (control). The sealed envelopes in each group were placed in a plastic container, marked 'STRATUM-1 (MALE)' and 'STRATUM-2 (FEMALE)' for male and female subjects to pick from respectively. This division into strata was done to enable equal representation of the two sexes in all the groups. Every patient picked an envelope (in a container) at random to determine his/her group, before entering the anaesthetic room.

The allocation was revealed to a nurse anaesthetist who opened the sealed envelope, filled the allocation sequence number and administered the required injection. The participants, surgeon, principal investigator and assistant involved in the outcome measurements were blinded to the allocation number and group of the subjects.

The local anaesthetic agent with the adjuvants/ placebo were constituted together and injected to the subjects by the nurse anaesthetist who had no further involvement in the study. The principal researcher entered the anaesthetic room as soon as the injection was given and measured upper lid and globe akinesia at 2, 5, 10, and 15minutes after the injection.

All the patients received a peribulbar local anaesthetic (L.A.) injection with 4.5ml of 2% lidocaine + 0.125mg/ml adrenaline given by an experienced Nurse anaesthetist. The three groups were:

Group A (Magnesium sulfate group) had an additional 80mg of Magnesium sulfate in 0.5mls of normal saline (N/S) added to the L.A.

Group B (Hyaluronidase group) had an additional 15.0 I.U. of hyaluronidase in 0.5mls of N/S to the L.A.

Group C (Control) had an addition of only 0.5mls of plain normal saline to the L.A.

All patients in the three groups received the same volume of local anesthetic mixture.

The eye was prepared with a 5% povidone iodine solution. Peribulbar anesthesia was done through two site injection technique (inferotemporal and superonasal) described by Davis and Mandel,[13] using a 25-gauge, 25 mm bevel disposable needle. Slight external manual pressure with 3-4 layers of gauze piece was applied over the eye immediately after injection.

Akinesia of globe was assessed by the principal investigator at 2, 5, 10 and 15 minutes after the peribulbar injection in four directions of gaze using 3-point scale for each direction. Scores were represented as: zero = complete akinesia, 1=limited movement and 2= full movement. Akinesia of orbicularis (upper eye lid) was also evaluated at 2, 5, 10 and 15 minutes using 3-points scale, were zero = complete akinesia/ flicker movement, 1= partial movement of upper eyelid, and 2=normal movement. Globe and lid akinesia scores were summed up to give total akinesia score

Post-operative globe akinesia was assessed every 15 minutes in four directions of gaze (superior, inferior, temporal and nasal) by principal investigator. The scores of the four directions were summed up until complete globe motility was restored (globe akinesia score of 8). Postoperative pain score was assessed at 30 minutes, 1 hour, 2 hours, 4 hours and 6 hours using a visual analogue scale (VAS) with a score range of 0-10 cm; zero cm representing no pain and 10 cm representing the most severe pain, by an assistant. Analgesic (500mg of paracetamol) was administered for a pain score of e"4cm. Total analgesic required for the first 6 hours was documented.

Operational definitions:

Lid akinesia: absent/or reduction of upper eyelid motility following injection of local anaesthetics into the orbit

Globe akinesia: abolition/reduction of globe motility due to injection of anaesthetics agent in the orbit

Duration of globe akinesia: the time between LA injections to full recovery from globe akinesia (full globe motility)

Globe akinesia score*:* was estimated by movement of globe in 4 directions (superior, inferior, temporal, and nasal), with maximum score of 8(0-2 for each gaze)

- 0 = No/flicker movement
- 1 =Reduced movement in the direction of gaze following a target
- 2 = Full movement in the direction of gaze following a target

Lid akinesia score*:* movement of upper eyelid in one direction (elevation of upper eyelid while following a target superiorly) giving a minimum of 0 and maximum of 2 score.

- 0 = No/flicker movement

- 1 =Reduced movement in the direction of gaze following a target
- 2 = Full movement in the direction of gaze following a target

Total akinesia score*:* summation of globe akinesia and lid akinesia scores (gives score range of 0- 10)

Successful anaesthetic block/adequate akinesia for surgery: attainment of total akinesia score (i.e. lid and globe akinesia scores) of ≤ 2)

Pain score*:* assessment of degree of pain on a scale of 0-10 cm (using visual analogue scale)

Analgesic rescue threshold*:* the pain score at which analgesic was administered (≥ 4cm)

Statistical analysis

Data obtained were coded and double entered into a computer software (excel). Data analysis was done with assistance of a statistician using Statistical Package for Social Sciences (SPSS) version 21 for windows (Chicago, Illinois).

Mean and standard deviation were calculated for age, weight, duration of surgery; duration of globe akinesia; akinesia score, time of successful L.A block and patient's pain score. Frequencies and percentages were determined for gender, eye operated, and recorded complications. Inferential statistical analysis was carried out using one-way analysis of variance (-ANOVA) or its equivalent in the case of failed normality test (Kluskal-Walli's one way ANOVA on rank) for quantitative data with post hoc test where there was significant difference. Frequencies (%) and Chi-square tests were used in comparison among categorical data.

RESULTS

A total of 150 participants completed the study out of 176 subjects who were initially enrolled. Subjects who could not complete the study were replaced by new recruits who randomly pick their allocation number returned to the plastic bowl. Patients' characteristics showed no statistically significant differences across the groups with regards to age, sex, weight, ethno-religious status and duration of surgery (Table 1).

The evaluation of the globe akinesia at (2), (5), (10), and (15) minutes after injection showed that the magnesium sulfate group had the lowest average globe akinesia score of 2.28±1.63, 0.76±1.08, 0.20±0.54, and 0.060±0.24 respectively in comparison to hyaluronidase and control groups. This difference was statistically significant (ANOVA on ranks, P<0.05, Table 2).

The average time to attain successful akinesia was least in the magnesium sulfate group (4.40±2.97 minutes) compared to other groups. This was statistically significant (p<0.001, one-way ANOVA (F) table 3).

Also, trend in cumulative number of subjects achieving successful akinesia (total lid and globe akinesia of 2 or less) at different time

Table 1: Comparisons of Patients' demographic characteristics across the three study groups

	$MgSO_4$	**Hyaluronidase**	**Control**	Test-F-	P-value
Age in years (Mean ± SD)	66.10±7.81	65.00±8.32	62.20±10.70	2.456	0.106
Gender (m/f)	25/25	25/25	25/25		
Weight(kilogram) (Mean ± SD)	60.40±10.30	62.50±9.35	64.90±6.50	2.216	0.117
Eye (R/L)	26/24		23/27	27/23	
Ethnicity No. (%)	**50 (100.0%)**	**50 (100.0%)**	**50 (100.0%)**	-X^{2}-	p-value
Hausa-Fulani	22 (44.0%)	23 (46.0%)	28 (56.0%)	2.950	0.815
Yoruba	6 (12.0%)	5 (10.0%)	4 (8.0%)		
Igbo	4 (8.0%)	7 (14.0%)	5 (10.0%)		
Other tribes	18 (36.0%)	15 (30.0%)	13 (26.0%)		
Religion No. (%)	**50 (100.0%)**	**50 (100.0%)**	**50 (100.0%)**		
Islam	30 (60.0%)	31 (62.0%)	36 (72.0%)	1.809	0.405
Christianity	20 (40.0%)	19 (38.0%)	14 (28.0%)		

Key: *R= right eye; L= Left eye; m=male, f= female*

Table 2: Comparison of Mean Globe akinesia score at different times of measurement (mean± SD)

	$MgSO_4$	Hyaluronidase	Control	P value	Post hoc test [a]
Globe Akinesia score at 2 minutes	2.28±1.63	3.68±2.66	3.10±1.27	0.002	P1=0.001 P2=0.018 P3=0.260
Globe akinesia score at 5 minutes	0.76±1.08	1.28±1.50	1.66±1.13	0.004	P1=0.069 P2<0.001 P3=0.040
Globe akinesia score at 10 minutes	0.20±0.54	0.52±0.93	0.94±1.06	<0.001	P1=0.089 P2<0.001 P3=0.008
Globe akinesia score at 15 minutes	0.060±0.24	0.24±0.56	0.44±0.67	0.005	P1=0.116 P2<0.001 P3=0.046

KEYS: ***a*** *= Tukey's* ***post-hoc test;*** *P1= comparison of magnesium sulfate versus hyaluronidase; P2= magnesium sulfate versus control; P3 = hyaluronidase versus control*

Table 3: Comparison of Mean time to achieve successful akinesia score (minutes), and duration of globe akinesia (Mean± SD)

Group	Magnesium Sulfate	Hyaluronidase	Control	(F)	p-value	[a] Post hoc test
Time of successful akinesia (minute)	4.40±2.97	7.24±4.17	7.52 ±3.87	9.424	<0.001	P1=0.002 P2<0.001 P3=0.809
Duration of globe akinesia P3=0.066 (minute)	167.12±22.72	138.26±16.82	129.90±16.89	53.541	<0.001	P1<0.001 P2<0.001

KEY: ***a*** *post hoc test comparisons: P1= magnesium sulfate versus hyaluronidase. P2= magnesium sulfate versus control; P3 = hyaluronidase versus control.*

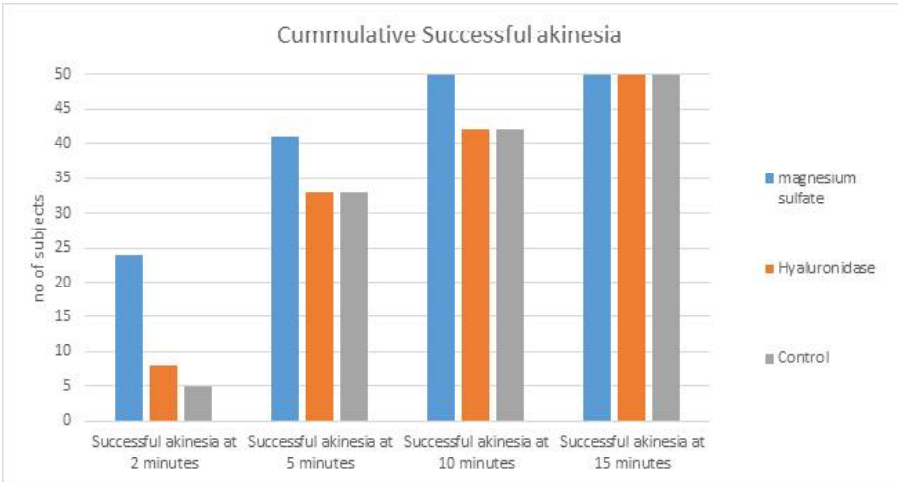

Figure 1: *Trend in cumulative number of patients who attained a successful akinesia) at different time intervals (2, 5, 10 and 15 minutes respectively). Onset of total akinesia was most rapid in the magnesium sulfate group.*

Table 4: Postoperative pain scores at 1/2hour, 1-hour, 2hours, 4-hours and 6-hours

	MgSO4 Group-50-	Hyaluronidase	Control group	-H-	P-value1
Post-operative pain score at ½ hour	1.12±0.56	1.22±0.48	1.18±0.77	2.584	0.275
Post-operative pain score at 1 hour	1.30±0.65	1.34±0.72	1.66±1.02	5.002.	0.082
Post-operative pain score at 2 hours	1.30±0.58	1.48±0.908	1.66±0.82	4.279	0.118
Post-operative pain score at 4 hours	1.52±0.64	1.62±0.75	1.72±0.82	0.219	0.896
Post-operative pain score at 6 hours	1.70±0.91	1.74±0.69	1.82±0.90	1.372	0.504

H=ANOVA on rank (or Kluskal Walli's test)

Table 5: Frequency of analgesic rescue required within 6 hours post-operation

	Magnesium sulfate	**Hyaluronidase**	**Control**	**Chi-square**	**P value**
No Analgesic	44(88.0%)	43(90.0%)	40(86.0%)		
Needed analgesic	6(12.0%)	7 (14.0%)	10(20.0%)	1.365	0.850
Amount needed					
1 tablet (500mg) of Paracetamol	4(8.0%)	5(10.0%)	7(14.0%)		
2 tablets (1000mg) of Paracetamol	2(4.0%)	2(4.0%)	3(6.0%)		
Total	**50(100.0%)**	**50(100.0%)**	**50(100.0%)**		

Table 6: Complications of anaesthetic injection

	Magnesium sulfate	Hyaluronidase	Control	P value
Absent	40(80.0%)	42(84.0.0%)	43(86.0%)	0.850
Present	10(20.0%)	8 (16.0%)	7(14.0%)	
Chemosis	6 (12.0%)	5 (10.0%)	4(8.0%)	
Subconjunctival haemorrhage	4 (8.0%)	3 (6.0%)	3(6.0%)	
Total	**50(100.0%)**	**50(100.0%)**	**50(100.0%)**	

intervals revealed that the onset of successful ocular akinesia was most rapid in the magnesium sulfate group (Figure 2)

The duration of globe akinesia was longest with the magnesium sulfate group (167.12±22.72 minutes) in comparison with the other groups. This difference was statistically significant ($p<0.001$, Table 3)

The postoperative pain score of the three groups at 1/2 hour 1-hour, 2hours, 4-hrs and 6-hours revealed no significant difference at various times as shown in table 4 ($p>0.05$ at different times, one-way ANOVA on ranks).

There was no systemic complication noticed among the participants. However, local complications like subconjunctival haemorrhage and chemosis were observed in the three groups. These complications involved 10 of the subjects in the magnesium sulfate group, 8 in the hyaluronidase, and 7 patients among the control group. This difference was not statistically significant. ($p=0.850$).

DISCUSSION

The average age of the subjects in this study was in the seventh decade, similar to the findings of other studies that were conducted on senile cataract patients. [4, 15] The males and females were equal in all the groups, which is due to the design of the study that ensured equal representation to avoid gender-related bias in pain perception. There was no significant difference in the ethnic and religious distribution among the three groups. Likewise, there was no significant difference in the average weight of the groups. These baseline characteristics are similar to reports of other studies. [4, 14]

The study showed the lowest scores with the magnesium sulfate group, followed by hyaluronidase, and highest in control group in the assessment of globe and lid akinesia scores at 2, 5, 10 and 15 minutes post L.A. injection. The observed difference was statistically significant among the magnesium sulfate and hyaluronidase groups compared to the control. Also, the time to attain successful akinesia was shortest in the magnesium sulfate group, followed by hyaluronidase, and then longest in the control group. This could imply that magnesium sulfate may cause better enhancement of early motor blockade than hyaluronidase. Hence, it may potentially reduce theatre waiting time and improve efficiency. The finding can be compared with similar studies by Mogahed *et al* [14] and El-Raouf *et al* [16] which found significant enhancement of the motor and sensory blocks in the magnesium sulfate group than in the placebo group. This is, however, contradictory to findings by Abu-Elyad *et al* [17] and Hamawy *et al* [18] which found no significant difference in the onset of ocular akinesia between magnesium sulfate adjuvant and placebo (ie without adjuvant) in peribulbar block for cataract surgery. This disparity may be due to differences in anaesthetic mixtures and doses used. For instance, this study used 80mg of magnesium sulfate while the study by Hamawy *et al* [16] used 50mg of magnesium sulfate as an adjuvant. The hyaluronidase group had a significantly lower globe akinesia score but surprisingly did not have a significant difference in the time to achieve successful akinesia in comparison with the control group. This finding is comparable to Schulenburg *et al*, [19] who found no significant effects of hyaluronidase on the onset of akinesia. However, Remy et al. [20] in Germany, found a significant decrease in the onset time of akinesia with hyaluronidase compared to the control subjects. It is noteworthy that differences in the various anaesthetic types, volumes, doses, and combinations used in our study compared to those used by different researchers in the previous studies may be responsible for the varied results.

The duration of globe akinesia, which is the time for full recovery of motor power was longer in the magnesium sulfate group (167.12±22.72 minutes), followed by the hyaluronidase group (138.02±16.38 minutes) and least in the control group (131.24±16.89 minutes). This significant finding implies that the $MgSO_4$ adjuvant has a better effect in enhancing the duration of the motor block than the hyaluronidase. Hence, it can aid in ensuring a longer duration of ocular motor block in the event of prolonged ocular surgery, especially with trainee surgeons. These results agree with a similar study by Mohamed *et al,* [21] who found that the time to full recovery of motor power was significantly longer in the magnesium sulfate group compared to the control group, suggesting that the addition of magnesium to the local anaesthetic mixture showed a clinical and statistically significant difference in the duration of motor block. Mogahed *et al* [14] equally found prolonged duration of ocular

akinesia with 50mg and 100mg of magnesium sulfate compared to the control group.

The pain score at 30 minutes, 1-hour, 2-hours, 4 hours, and 6-hours post-operative periods revealed no significant difference between the three groups. In the same vein, the amount of analgesic requested for the corresponding period showed no significant difference among the 3 groups. This could imply that both magnesium sulfate and hyaluronidase added as adjuvant in LA have no postoperative analgesic advantage over one another, and with respect to control in the studied population. This is divergent from the findings of El-Raouf *et al* [14] who found that the addition of 50mg magnesium sulfate to an anaesthetic agent caused a significant reduction in pain score immediately and at 6 hours post-operatively using the VAS as used in this study. Similarly, the study by El-Hamid, [22] showed lower pain score with magnesium sulfate adjuvant. Furthermore, Mogahed *et al,* [14] showed significantly lower postoperative VAS pain score and fewer analgesic rescue requests with the magnesium sulfate adjuvant group compared to the control. These contradictory reports might be due to differences in anaesthetic mixtures/doses used and pain score cut-off point differences for analgesic administration in the study design. Also, socio-cultural, racial and geographic differences in pain threshold and level of understanding of the pain assessment tool could be possible reasons for these contrasting findings. For instance, our study involved an older population of people above 50 years, while the above studies included people below 50 years.

CONCLUSION

Magnesium sulfate and hyaluronidase can enhance earlier onset of akinesia. Magnesium sulfate prolonged the duration of the motor block of the globe more than hyaluronidase. This could provide suitable conditions for surgery, especially for procedures that require a longer duration. Magnesium sulfate may be an effective alternative to hyaluronidase in low income settings.

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Conflicts of interest
There are no conflicts of interest.

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