Original Article

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Comparison of the efficacy of atracurium pretreatment versus magnesium sulphate for prevention of suxamethonium-induced fasciculation and post-operative myalgia

***Folami, E.O.[1], Olajumoke, T.O.[2], Kolawole, I.K.[3], Ojo, A.K.[4], Raji, S.A.[2], Folami, R.O.[5]**

Abstract

Background: Suxamethonium remains the best option for rapid sequence induction, it is the only depolarizing muscle relaxant in clinical use. However, fasciculation and myalgia are frequent adverse effects of the drug. Myalgia can last for several days with associated discomfort. Non-depolarizing muscle relaxant and magnesium sulphate have been tried as pretreatments to attenuate the fasciculation and myalgia with varying results.

Methods: A double blind, randomized study of 100 adult surgical patients of ASA I or II Class were recruited to receive either intravenous atracurium (0.05mg/kg) (Group A) or intravenous magnesium sulphate (30mg/kg)(Group B). The occurrence, severity and duration of fasciculation as well as the occurrence and severity of post-operative myalgia were also recorded.

Results: Muscle fasciculation occurred in 39 (78%) patients in Group A and 27(54%) patients in Group B (p= 0.001). The severity of fasciculation was mild to moderate in Group B while Group A in addition also recorded some cases of severe episodes of fasciculation. Mean duration of fasciculation in Group A was longer (28.48 ± 1.07sec) than in group B (19.44± 1.93seconds) (p= 0.001). Post-operative myalgia was not experienced at 6hrs and 48hrs, while 2 patients (1 in each Group) had it at 12hrs. At 24hrs, post-operative myalgia was present in 13(26%) patients in group A and 5(10%) patients in group B, (p=0.043). The severity of post-operative myalgia recorded both at 12hrs and 24hrs was mild.

Conclusion: Magnesium sulphate demonstrated better efficacy at reducing fasciculation and post-operative myalgia than atracurium

Keywords: Suxamethonium, Fasciculation, Myalgia, Atracurium, Magnesium Sulphate

***Corresponding author**
Folami, E.O.
ORCID-NO: https://orcid.org/0000-0003-1503-1208
E-mail: emmanuel.folami@uniosun.edu.ng

[1]Faculty of Clinical Sciences, Osun State University, Osogbo, Nigeria
[2]Faculty of Clinical Sciences, LAUTECH, Ogbomoso, Nigeria
[3]Faculty of Clinical sciences, University of Ilorin, Ilorin, Nigeria
[4]Faculty of Clinical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria
[5]Faculty of Basic medical Sciences, Osun State University, Osogbo, Nigeria

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Comparaison de l'efficacité du prétraitement à l'atracurium par rapport au sulfate de magnésium pour la prévention de la fasciculation induite par le suxaméthonium et de la myalgie postopératoire

***Folami, E.O.[1], Olajumoke, T.O.[2], Kolawole, I.K.[3], Ojo, A.K.[4], Raji, S.A.[2], Folami, R.O.[5]**

Contexte général de l'étude : Le suxaméthonium reste la meilleure option pour l'induction en séquence rapide, c'est le seul myorelaxant dépolarisant utilisé en clinique. Cependant, la fasciculation et les myalgies sont des effets indésirables fréquents du médicament. La myalgie peut durer plusieurs jours avec une gêne associée. Des relaxants musculaires non dépolarisants et du sulfate de magnésium ont été essayés comme prétraitements pour atténuer la fasciculation et la myalgie avec des résultats variables.

Méthode de l'étude : Une étude randomisée en double aveugle de 100 patients chirurgicaux adultes de classe ASA I ou II a été recrutée pour recevoir soit de l'atracurium intraveineux (0,05 mg/kg) (groupe A) soit du sulfate de magnésium intraveineux (30 mg/kg) (groupe B). La survenue, la sévérité et la durée de la fasciculation ainsi que la survenue et la sévérité des myalgies postopératoires ont également été enregistrées.

Résultats de l'étude : Une fasciculation musculaire s'est produite chez 39 (78 %) patients du groupe A et 27 (54 %) patients du groupe B (p = 0,001). La sévérité de la fasciculation était légère à modérée dans le groupe B tandis que le groupe A a également enregistré quelques cas d'épisodes sévères de fasciculation. La durée moyenne de fasciculation dans le groupe A était plus longue (28,48 ± 1,07 s) que dans le groupe B (19,44 ± 1,93 s) (p = 0,001). La myalgie postopératoire n'a pas été ressentie à 6h et 48h, alors que 2 patients (1 dans chaque groupe) l'ont eu à 12h. A 24h, des myalgies postopératoires étaient présentes chez 13(26%) patients du groupe A et 5(10%) patients du groupe B, (p=0,043). La sévérité des myalgies postopératoires enregistrées à la fois à 12h et à 24h était légère.

Conclusion: Magnésium le sulfate a démontré une meilleure efficacité pour réduire la fasciculation et les myalgies postopératoires que l'atracurium.

Mots-clés : Suxaméthonium, fasciculation, myalgie, atracurium, sulfate de magnésium

***Corresponding author**
Folami, E.O.
ORCID-NO: https://orcid.org/0000-0003-1503-1208
E-mail: emmanuel.folami@uniosun.edu.ng

[1]Faculty of Clinical Sciences, Osun State University, Osogbo, Nigeria
[2]Faculty of Clinical Sciences, LAUTECH, Ogbomoso, Nigeria
[3]Faculty of Clinical sciences, University of Ilorin, Ilorin, Nigeria
[4]Faculty of Clinical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria
[5]Faculty of Basic medical Sciences, Osun State University, Osogbo, Nigeria

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INTRODUCTION

Suxamethonium is the only depolarizing muscle relaxant and has been in use for over six decades because of its low cost, fast onset of action, excellent muscle relaxation, and quick recovery (1). However, its two side effects - fasciculation and postoperative myalgia – restrict its use in clinical practice (2). Fasciculation is the involuntary intermittent muscle contraction while postoperative myalgia is muscle pain resulting from such fasciculations or following strenuous exercise. Suxamethonium binds to nicotinic receptors at the neuromuscular junction and opens the ligand gated channels in the same way as acetylcholine, which results in prolonged depolarisation with sustained muscle contraction. Non- depolarising muscle relaxants (Atracurium being an example) are the commonest agents for pre-treatment to minimize fasciculation and postoperative myalgia however patients usually complain of diplopia, difficulty in breathing and voice changes before induction of anesthesia (3). These issues associated with non-depolarising muscle relaxants necessitated the need to explore other agents. The other agents that have been used with varying results include; magnesium sulphate (4-6), pregabalin (7), diazepam (8), ketamine (9), lidocaine (10), vitamin C (11), calcium gluconate (12) and diclofenac sodium (13). In a meta-analysis of some controlled studies, the incidence of fasciculation was as high as 95% and that of myalgia at 24hrs was 50% (14).

With the availability of sugammadex, rocuronium is a possible alternative to suxamethonium. Although rocuronium shows less side effects than suxamethonium, it cannot completely replace suxamethonium which has distinctive characteristics of low cost, efficient muscle relaxation and short duration of action. Management of laryngospasm is one of the lifesaving intervention that is ascribed to suxamethonium where it can be administered intramuscularly, intraosseously and sublingually without necessarily having to secure intravenous access (15). These almost irreplaceable features of suxamethonium necessitated the search to ameliorate its side effect in clinical practice rather than eliminating the drug. This study compared the efficacy of pretreatment with atracurium versus magnesium in the prevention of suxamethonium induced fasciculation and postoperative myalgia by measuring the incidence of fasciculation, duration of fasciculation, severity of fasciculation, incidence of myalgia and severity of myalgia.

METHODS

This is a randomised clinical study that was conducted after approval from UNIOSUN Teaching Hospital Research Ethics Committee. Written informed consent was obtained from patients scheduled for elective surgeries under general anesthesia.

One hundred patients, aged 18-60 years, of either sex, ASA physical status I and II scheduled for elective surgeries requiring general anesthesia were recruited into the study. Patients were instructed on the use of Visual Analogue Scale (VAS). Exclusion criteria included patients with previous family history of high fever following anesthesia, pregnant patients, patients with contraindications to suxamethonium (burns, neuromuscular diseases, paraplegia) and patients on calcium channel or beta blockers. The patients were randomly allocated to two groups with the help of a computer generated table of random numbers to receive following drugs:

Group A received intravenous atracurium at 0.05mg/kg in 10mls dilution as pretreatment while Group B received intravenous magnesium sulphate at 30mg/kg in 10mls dilution. All patients were fasted overnight and received 10mg metoclopramide and 10mg diazepam orally at night; and were pre - medicated with same 2hrs before surgery. The study drugs were given to the Anesthetist in training who did not know the content of the syringe.

In the operating room, with patient on the operating table and after the basic monitors were attached, induction of anesthesia was with a sleep dose of propofol, followed by 0.1mg/kg morphine patients were then given the study medications according to the numbers allotted to them and as calculated by the Anesthetist in training. Three minutes after pre-treatment, the patients were then given suxamethonium at 1.0mg/kg. Intensity and duration of fasciculations after suxamethonium were assessed by the researcher (who was blinded to the drug given). Severity was assessed on a 4 point scale as: nil=no visible fasciculation, mild=very fine fingertip or facial movement, moderate=minimal fasciculation on trunk and extremities, severe=vigorous fasciculation on trunk and extremities.

Intubation was done with an appropriate sized cuffed endotracheal tube and ventilation was adjusted to maintain normocapnia. Maintenance of anesthesia was with 1-2% isoflurane in oxygen enriched air for continued hypnosis and iv pancuronium at 0.1mg/kg as

muscle relaxant. Intermittent doses of pancuronium 2mg per dose were administered during surgery as indicated. At the end of the surgery, neuromuscular blockade was reversed with neostigmine and atropine (to obtund its muscarinic effects), extubation was done following pharyngeal suction, and patient was transferred to the post anesthesia care unit (PACU) after adequate recovery from anesthesia.

The postoperative analgesia given was 1gm of paracetamol infusion. The fitness of patient to leave PACU for the ward was determined using New Aldrete Scoring System and Visual Analogue Scale.

Patients were transferred to the ward with minimum Aldrete score of 12 and VAS of <4. Intramuscular diclofenac 75mg was given as rescue analgesia if VAS was greater than four (4). Post-op myalgia was assessed by the researcher using the four point scale at 6hrs, 12hrs, 24hrs and 48hrs (0- Absence of muscle pain, 1-Pain limited to one area of the body, 2-Pain involving more than one area of the body, 3-Generalized muscle pain). The results obtained from the study were subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS, version 20.0 SPSS Inc., Chicago, Illinois, USA).

The categorical data such as age, sex and severity of fasciculation were analysed using frequencies and percentages. The test of association was done using chi-square. Continuous data such as weight, BMI, and duration of fasciculation were presented as mean and standard deviation and subjected to student t-tests. Level of significance was set at p-value < 0.05 for all statistical analysis.

RESULTS

One hundred patients with ASA physical status I and II, with fifty patients in each group, were recruited for the study between February 2019 and July 2019. Data from thirty-seven (37%) males and sixty three (63%) females were analyzed. All the patients completed the study. There were no significant differences between the two groups with respect to age, sex, ASA physical status, weight, height and body mass index (p>0.05) (Table 1).

The incidence of muscle fasciculation was 78% in group A and 54% in group B (p=0.001) (Table 2). The intensity of muscle fasciculations were mild (23.1%), moderate (64.1%) and severe (12.8%) in group A. While group B had mild (66.7%) and moderate (33.3%) fasciculations without a single patient with severe fasciculation (p=0.001). The mean duration of fasciculations in group A (28.48 ± 1.07 seconds) was more than what was observed in group B (19.44 ± 1.93 seconds) (p= 0.001).

Within the first 6hrs and at 48hrs, postoperative myalgia was not experienced in any patient in both groups A and B. Postoperative myalgia occurred at 12hrs and 24hrs only and they were mild. At 12 hours, the incidence of postoperative myalgia was 2% in each of the groups (p = 0.869). At 24hrs, the incidence of myalgia was 26% and 10% for group A and group B respectively (p=0.043).

DISCUSSION

The results showed that pretreatment with 0.05mg/kg atracurium and 30mg/kg magnesium sulphate has the ability to reduce fasciculation and post-operative myalgia induced by suxamethonium. However, magnesium sulphate demonstrated better efficacy than atracurium in reducing the incidence, duration and severity of fasciculation, as well as post-operative myalgia. The superior efficacy demonstrated by magnesium sulphate pretreatment may be due to its cell membrane stabilizing effect, ability to inhibit NMDA receptors and to increase the production of vasodilator prostaglandin which could account for reduced fasciculation in musculoskeletal system, and consequently post-operative myalgia.

In a meta-analysis done by Schreiber and co-workers (14), the incidence of fasciculation ranged from 0-100%. However, in this study, atracurium pretreatment lowered the incidence of fasciculation to 78% while magnesium sulphate pretreatment lowered it further to 54%.

The atracurium group of this study had a higher incidence of fasciculations compared to Famewo (16) and Paganni (17). Famewo (16) used various doses of IV atracurium (ranging from 0.035 to 0.075mg/kg) and found the incidence to be 0 - 40%. However, he advised that 0.05mg/kg gave the best result. Paganni and colleagues (17) on the other hand used a higher single dose of intravenous 5mg atracurium across board and reported a lower incidence of fasciculation in their study. If we assume an average weight of an adult to be 70kg, Paganni's (17) dosage will be 0.07mg/kg which is higher than the dose in this study. The higher dose used therefore, may be responsible for the lower incidence of fasciculation (44%) in their study.

In another study by Fatemeh and Mojgan (18), the overall high incidence of moderate and severe forms of fasciculation, may be due to the

lower dose of atracurium used. Lower doses of atracurium, as used in this study, are known to cause a higher incidence of fasciculations (14). It could however also be due to increased genetic susceptibility to suxamethonium-induced fasciculation in the African population compared to the Middle East population, which formed the genetic pool used by Fatemeh and Mojgan (18).

The Incidence of fasciculation in the magnesium sulphate pretreatment group of Danladi and colleague's study was 81% and that of Das *et al* was 63.3% (19). These values were higher than the findings in the magnesium group of this index study (54%) despite the use of a similar dose of magnesium sulphate (30mg/kg) for pretreatment in Danladi study and double dose (60mg/kg) in Das *et al* (20).

Propofol and magnesium have been documented separately to be effective when used alone to reduce fasciculation. Propofol alone as a bolus or repeat bolus injection has been reported to reduce the incidence of suxamethonium-induced fasciculations by Garg *et al* (21). In that study, increased dose of propofol reduced incidence of fasciculation. The probable synergy of propofol and magnesium sulphate would have further contributed to the reduction in the incidence of fasciculation in this present study.

In common with the index study, Kumar *et al* (22) used propofol as induction agent in their study, but with a slightly higher dose of magnesium sulphate for pretreatment (40mg/kg). They got an incidence of 50% fasciculations which is slightly lower than the value recorded in this study. This difference may be attributed to the higher dose of magnesium sulphate (40mg/kg) used in their study. This is in agreement with Gray *et al* (23) who demonstrated the dose-dependent therapeutic vasodilatory effects of magnesium sulphate in preterm male and female. The use of various forms of opioid agents have been linked to lower incidences of suxamethonium-induced fasciculation. This may therefore contribute to the lower incidence of fasciculation recorded in this study, as also observed in Kumar *et al* (22) and Das *et al* (20) studies. The absence of severe fasciculation in this index study is similar to the findings of Kumar *et al* who also found absence of severe fasciculation (22), thus demonstrating the fact that the combination of propofol-magnesium has the ability to prevent severe form of fasciculation.

Shoroghi and colleagues (24) reported that pretreatment before administration of suxamethonium has the ability to reduce the duration of fasciculation which is similar to the result obtained in this index study. However, the duration of muscle fasciculation in patients who were pretreated with atracurium was found to be significantly longer ($P<0.001$) compared to those who had pretreatment with magnesium sulphate. Therefore, magnesium sulphate group demonstrated better reduction in duration (19.44±9.93sec) compared to (28.48±1.07sec) observed in the atracurium group. This demonstrated that magnesium sulphate does not only reduce the incidence and intensity of fasciculation better than atracurium, it is also superior to atracurium in reducing the duration of fasciculation when used as a pretreatment.

The incidence of post-operative myalgia due to suxamethonium varies as high as 90% and was generally thought to be approximately 50% with placebo (14). A study done by Mingus and colleagues (25) reported that post-operative myalgia appeared to be unrelated to the use of suxamethonium alone. This is in agreement with Schreiber (26) who reported that the origin of post-operative myalgia is complex with diverse pathogenesis. The commonly used method of preventing myalgia is the use of a non-depolarizing muscle relaxant as a pretreatment which has been demonstrated to be efficacious in achieving this aim.

The incidence of postoperative myalgia over 24 hour's assessment was 26% in atracurium group and 10% in magnesium group which was lower than the 50% obtained in the Schreiber meta-analysis (14). The 26% incidence of myalgia at 24hrs with the use of atracurium at a dose of 0.05mg/kg in this study is slightly lower than that reported by Paganni and colleagues (17) in which the incidence was 36%. The expectation would have been a better reduction in myalgia incidence in Paganni study (17) because of the lower incidence of fasciculation attributable to the higher dose of atracurium (0.07mg/kg > 0.05mg/kg) used for the pre-treatment, but the result showed otherwise. Nevertheless, it can be inferred from this index study that pretreatment with atracurium has the ability to reduce postoperative myalgia in contrast to the report of Fatemeh and Mojgan (18) that showed that atracurium pretreatment did not affect myalgia.

Kumar *et al* (22) recorded no patient with myalgia in their series when magnesium sulphate was used for pretreatment compared to the index study, even though they used a higher dose of suxamethonium (1.5mg/kg). The difference in findings may be due to a higher dose of magnesium used in their series, (40mg/kg vs

30mg/kg), which resulted in slightly lower incidence of fasciculation compared to the value recorded in this study (50% vs 54%).

Das *et al* (20) also had a higher incidence of myalgia (30%) with magnesium sulphate pretreatment compared to the index study probably due to a higher incidence of fasciculation seen in the magnesium sulphate group in their study (63.3% vs 54%). There was also a reduction in the incidence of myalgia in this index study when compared to the 50% recorded in the meta-analysis by Schreiber and colleagues (14).

Limitation: The visual assessment of fasciculation is subjective. The objective assessment by measuring the increase in myoglobin and creatinine phosphokinase at the laboratory would have been more accurate but the facility is not available in our hospital.

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CONCLUSION

Magnesium sulphate is more efficacious than atracurium in reducing the incidence, intensity and duration of fasciculation and postoperative myalgia. Furthermore, the double combination of magnesium sulphate and propofol have more potentiating effect in decreasing the incidence and severity of suxamethonium-induced fasciculation and postoperative myalgia.

Conflict of interest: None

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Table 1. Demographic and clinical characteristic of patients

Variable	Group A n(%)	Group B n(%)	Total	X^2 value	P value
Age Group					
<50yrs	40(80.0)	27(54.0)	67(67.0)	1.741	0.628
=50yrs	10(20.0)	23(46.0)	33(33.0)		
Sex					
Male	19(38.0)	18(36.0)	37(37.0)		
Female	31(62.0)	32(64.0)	63(63.0)	0.043	0.836
ASA					
1	30(60.0)	35(70.0)	65(65.0)		
2	20(40.0)	15(30.0)	35(35.0)	1.099	0.293
Anthropometric measurement					
	Mean ± SD	Mean ± SD		t-value	p-value
Weight	61.43 ±6.46	62.32 ± 7.28		0.647	0.519
Height	1.62 ±0.07	1.63 ±0.06		0.218	0.828
Body mass index	23.12 ±2.11	23.36 ±2.12		0.458	0.648

ASA: American Society of Anesthesiologists

Table 2: Incidence and severity of fasciculation in the groups

Variable	Group A n (%)	Group B n (%)	X^2 value	p-value
No fasciculation	11(22.0)	23(46.0)		
Incidence of fasciculation	39(78.0)	27(54.0)		
Total	50(100)	50(100)	16.227	<0.001*
Severity of fasciculation				
Mild	9(23.1)	18(66.7)		
Moderate	25(64.1)	9(33.3)		
Severe	5(12.8)	0		
Total	39(100)	27(100)	26.043	<0.001*
Severe			- -	
<50yrs	5(100.0)	0		
=50yrs	0	0		
Total	5(100.0)	0		

Table 3: Duration of fasciculation among the groups

Variable Time(secs)	Group A n (%)	Group B n (%)	X^2 value	P value
No fasciculation	11(22.0)	23(46.0)		
11-20 secs	15(30.0)	17(34.0)		
21-30 secs	13(26.0)	9(18.0)		
>30 secs	11(22.0)	1(2.0)	29.583	<0.001
Total	50(100.0)	50(100.0)		
	Mean ± SD	Mean ± SD	t value	P value
	28.48±1.07	19.44±1.93	4.093	<0.001

Table 4: **Incidence and severity of postoperative myalgia among the groups**

Time		Group A n(%)	Group B n(%)	X^2 value	P value
Mild					
6 HOURS	YES	0(0)	0(0)		
	NO	50(100.0)	50(100.0)	-	-
	TOTAL	50(100.0)	50(100.0)		
12 HOURS	YES	1(2.0)	1(2.0)		
	NO	49(98.0)	49(98.0)	0.998	0.869
	Total	50(100.0)	50(100.0)		
24 HOURS					
	YES	13(26.0)	5(10.0)	4.256	0.043*
	NO	37(74.0)	45(90.0)		
48HOURS	Total	50(100.0)	50(100.0	-	-
	YES	0(0)	0(0)		
	NO	50(100.0)	50(100.0)		
	TOTAL	50(100.0)	50(100.0)		

NB: All forms of myalgia were mild