


Efficacy of 48 hours dose of phenytoin in prevention of early post-traumatic seizure

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ABSTRACT

Background Antiseizure medications, such as phenytoin sodium, have been shown in some reports to reduce the incidence of early post-traumatic seizure. These medications, however, are not without side effects which may be dose related or duration related. The risks associated with short-term therapy are minimal and often dose related (and hence avoidable). This study intends to determine the efficacy of a short-course (48-hour dose) of phenytoin in prevention of early post-traumatic seizure.

Methods This was a prospective randomised double-blind clinical intervention study. Head injured patients presenting within the first 24 hours were randomly assigned to either 48-hour dose of phenytoin or control groups, and were observed for clinical seizure over a week. The difference in the incidences of early post-traumatic seizure between the two groups was determined by χ^2 test. A $p < 0.05$ was considered as statistically significant.

Results A total of 94 patients were included in the study, 47 each in the control group and the phenytoin group. There were 77 males and 17 female (M:F 4.5:1). Both groups had similar demographic and clinical profile. The incidence of seizure was 21.3% in the control but 2.1% in the treatment arm ($p < 0.01$). All seizures occurred within 24 hours of trauma in the control, while the only episode of seizure in the treatment group occurred later.

Conclusion A short-course (48-hour dose) of phenytoin might be an effective prophylactic treatment to reduce the incidence of early post-traumatic seizure.

INTRODUCTION

Post-traumatic seizures are one of the important but poorly understood sequelae of head injury (HI), or, more specifically, traumatic brain injury (TBI).¹ They can occur either early (within 1 week of the injury) or late (from 1 week to years after the trauma).¹ The particular significance of early post-traumatic seizures (EPTS) lies in the fact that a seizure attack within the acute stage of HI may result in brain hypoxia, triggering cerebral hyperaemia, increased neuronal metabolic demand, increased release of proinflammatory and excitotoxic neurotransmitters, and, finally raised intracranial pressure (ICP) and secondary brain damage; all

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early post-traumatic seizure (EPTS), a sequelae of traumatic brain injury (TBI) with peak incidence in the first 24 hours of trauma, may be curtailed by prophylactic antiseizure medication.

WHAT THIS STUDY ADDS

⇒ Prophylactic phenytoin administration limited to the first 48 hours of trauma may be sufficient for the purpose of reducing the incidence of EPTS following TBI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a platform for further comparative studies, possibly using other common agents for seizure prophylaxis in TBI, to interrogate the effectiveness of limiting prophylaxis for EPTS to the period of greatest risk, with a view to reducing the cost of care and side effects of antiseizure medications.

together leading to higher morbidity and mortality.^{2,3}

Because post-traumatic seizures have such negative impact on outcome, patients with TBI are routinely given preventive antiseizure medications by some clinicians.⁴ However, there is only conflicting evidence to show that prophylactic antiseizure medications have the ability to reduce the incidence of EPTS.^{1,5} What is more, there are documented potential complications of the use of these drugs in the brain-injured patients. For instance, there are some animal data documenting that early treatment with benzodiazepines impairs both neuroplasticity and fundamental brain repair processes.⁶ Phenytoin and carbamazepine, each a common antiseizure medication in clinical use, have also been shown to impact negatively on cognitive performance in patients who received these agents for seizure prophylaxis after brain injury.⁷ In high-resource settings, levetiracetam is now largely preferred to phenytoin for post-traumatic seizure prophylaxis, partly because of better side effect profile.



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In our own part of the world, that is, Nigeria, a low/middle-income country in sub-Saharan Africa, there is no known national clinical protocol on antiseizure-prophylaxis in patients with TBI and this modality, to our knowledge, is not practised by the majority of our neurosurgical centres. In our practice, specifically, antiseizure-prophylaxis in patients with TBI is not practised, rather antiseizure medications are commenced therapeutically only after onset of seizure in each case.

The cost of procuring these medications is another consideration in our privately funded healthcare system. Here, the patients, most of whom live below the poverty line, pay out-of-pockets for all the expenses of their in-hospital care. In addition, levetiracetam is more expensive (>20 times) and less widely available than phenytoin. Therefore, the latter is still the first drug of choice widely used in the management of seizures, including post-traumatic ones, in our own practice.

Whereas it might be prudent to avoid long-term phenytoin prophylaxis in patients with TBI based on of the efficacy data and risks associated with its use; but since the risks associated with short-term therapy are often dose related (and hence avoidable) and because about half to two-thirds of EPTS occur in the first 24 hours, short-term phenytoin therapy might be a pragmatic choice after all.^{4,8}

This study aims to evaluate the effectiveness of a short-course (48-hour dose) prophylactic administration of phenytoin, a relatively cheap and widely available antiseizure medication in our setting, in prevention of EPTS in a cohort of patients with TBI.

METHODS

Setting

The University College Hospital Ibadan is the premier teaching hospital in our country. It is located in Ibadan, the largest and one of the most densely populated cities in Nigeria. It is a thousand-bed hospital, has the first and the largest neurosurgical department and is a major referral centre for neurosurgical cases in our country.⁹ In-hospital healthcare costs in Nigeria are still predominantly privately funded by out-of-pocket payments at each point of service. With this model of healthcare financing, background endemic poverty and logistic problems, HI patients are not infrequently managed without the required neuroimaging and intensive care unit admission.¹⁰

Data collection and analysis

This was a prospective randomised double-blind clinical intervention study. The participants were patients with HI who presented at our centre within 24 hours of trauma in a half-year period between June and December 2017. The patients presenting after 24 hours of trauma, those with onset of seizure before presentation, patients with previous cranial neurosurgical procedures or HI,

pretrauma history of seizure and pregnant women were excluded. A sample size of 88 patients (44 patients in each group) was calculated using the formula for estimation of the difference between two population proportions with a power of 80%, a two-sided level of significance of 5% and an attrition rate of 10%.

All the patients in the study were initially managed clinically according to the standard treatment protocols for managing HI at our facility. HI was classified using the Glasgow Coma Scale (GCS) score into mild (GCS 13–15), moderate (GCS 9–12) and severe (GCS 3–8). The patients were then randomly assigned to either phenytoin or control groups by a senior registrar who was not a member of the research team using a table of random numbers to generate allocation sequence. Our patients' population size was numbered 01–94. The phenytoin group was determined by blindly locating a point on the table of random numbers and selecting consecutive blocks of numbers whose first two digits fell between 01 and 94 while progressing down the columns. The rest of the unselected numbers between 01 and 94 were assigned to the control group. The patients in the phenytoin group were given a loading dose of 15 mg/kg body weight of intravenous phenytoin. They then received a third of 5 mg/kg body weight/day of intravenous phenytoin every 8 hours until 48 hours of admission.^{11,12} The control group had normal saline administered in place of phenytoin. The blood samples for serum phenytoin determination in the phenytoin group were taken 3 hours after the loading dose of phenytoin.

The patients were observed for seizures over a period ending on the seventh day after trauma; the primary outcome, thus, being the incidence of EPTS in the patient cohort. For reasons of logistic limitations, the diagnosis of seizures was by clinical observation only. Seizure was defined as episodes of focal or generalised repetitive jerky movements, rigid violent muscle contraction/spasm, upward rotation of the eyes, sustained deviation of the eyes or head to one side, staring spells, sudden fall or posturing with or without small gusts of respiration or frothing of saliva.¹³ The occurrence of seizure was usually observed for in our practice by any of the members of the neurosurgery team, casualty medical officers and nursing staffs, and sometimes, even by patients' relatives. The nursing staff also usually maintain seizure charts for such patients of interest.

The statistical significance of the difference in the rates of EPTS between the two study groups was determined with the Chi-square test. A p-value less than 0.05 was considered as statistically significant.

RESULTS

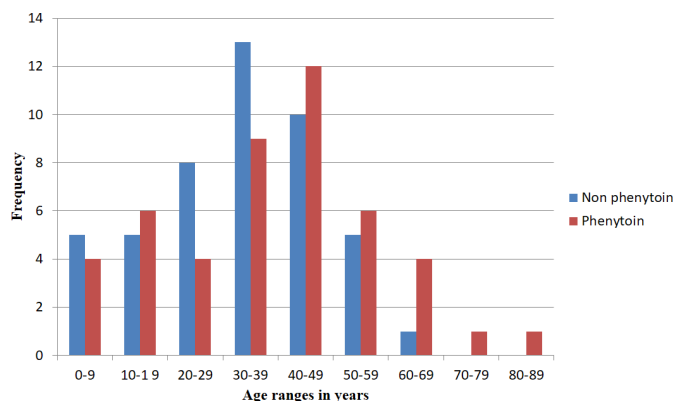
A total of 94 patients were included in the study, 47 each in the control, non-phenytoin arm (group A) and the treatment, phenytoin arm (group B). Both groups had similar demographic and clinical profiles (table 1). There were 77 males and 17 females (M:F 4.5:1), 39:8 in group

Table 1 A randomised study on the effectiveness of prophylactic phenytoin for preventing post-traumatic seizure: patients clinical demographics

	Total N=94	Phenytoin N=47	Non-phenytoin N=47	P value
Age, mean (SD)	34.4 (17.5)	37.0 (18.5)	31.8 (16.2)	0.789
Age group, N (%)				0.6
15 and below	17 (18.1)	8 (17.0)	9 (19.1)	
Above 15	77 (81.9)	39 (83.0)	38 (80.9)	
Gender, N (%)				
Male	77 (81.9)	38 (80.9)	39 (83.0)	0.789
Female	17 (18.1)	9 (19.1)	8 (17.0)	
Head injury severity, N (%)				
Severe	19 (20.2)	10 (21.3)	9 (19.1)	0.806
Moderate	20 (21.3)	9 (19.1)	11 (23.4)	
Mild	55 (58.5)	28 (59.6)	27 (57.5)	
Cranial CT scan, N (%)				
Yes	56 (59.6)	29 (61.7)	27 (57.4)	0.752
No	38 (40.4)	18 (38.3)	20 (42.6)	

A and 38:9 in group B. The age ranged from 1 to 83 years in the total study population, 1–65 years in group A and 2–83 years in group B. The mean age of the total study population was 34.4±17.5 years, 31.8±16.2 years in group A and 37.0±18.5 years in group B ($p=0.789$). The peak age incidence of HI was in the 30–49 years age groups among the total study subjects, accounting for 46.8% of the cases and representing 49% in group A and 44.6% in group B (figure 1). Seventeen of the 94 patients (18.1%) were 15 years or less.

Severity of HI was similar in both groups, $p=0.806$, table 1 showing the varying proportional distributions of the mild, moderate and severe extents thereof. Because of economical reason, a cranial CT scan was obtained in 59.6% (56/94) of the patients, 57.4% (27/47) in group A and 61.7% (29/47) in group B. The cranial CT scan showed haemorrhagic contusions in 42.9% (24/56) of the cases, acute subdural haematoma in 21.4% (12/56) and intracerebral haemorrhage

**Figure 1** Prophylactic phenytoin for post-traumatic seizures: age distribution of the patients in years.

in 17.9% (10/56) of the patients (table 2). There was no statistically significant difference in the clinical and demographic characteristics between the cohort with CT and those without (table 3).

The overall incidence of seizure was 11.7%, being 21.3% in group A (the control arm) and 2.1% in group B, the treatment arm of the study ($p=0.008$) (figure 2). There was no difference in the proportional incidence between the genders (table 4).

All seizures occurred within the first 24 hours of trauma in group A while the only episode of seizure in group B, the treatment arm of the study occurred on the seventh day post-trauma. The mean duration of onset of seizure in group A was 4.8 hours from trauma with 60% of these occurring within the first 4 hours and none later than 12 hours (figure 3). The seizure was focal in one patient (9.1%) and generalised in the other 10 patients (90.9%). Seizures occurred more frequently in children and with increasing severity of HI (tables 4 and 5). The population with seizures accounted for 55.6% of the patients who were 15 years and below in group A, the controls (figure 4). The only case of seizure in group B, the phenytoin-treated arm, occurred in a 10-year-old. The mean serum phenytoin level in group B was 59.7±17.3 µmol/L (therapeutic range=39.6–79.2 µmol/L). The serum phenytoin was within the therapeutic range in 76.6% (36/47) of the patients in group B, below the therapeutic range in 12.8% (6/47) and above the range in only 10.6% (5/47). In the only case of seizure in group B, the serum phenytoin was within the therapeutic change. One of the patients in group B (2.1%) had local irritation at the phenytoin infusion site; otherwise no other adverse effect of phenytoin was seen in this study. The mortality rate at the end of 1-week observation was 8.51%

Table 2 A randomised study on the effectiveness of prophylactic phenytoin for preventing post-traumatic seizure: cranial CT scan findings

Morphology N (%)	Total N=56	Phenytoin N=29	Non-phenytoin N=27	P value
Depressed skull fracture	3 (5.4)	2 (6.9)	1 (3.7)	1.000
Subdural haematoma	12 (21.4)	5 (17.2)	7 (25.9)	0.536
Extradural haematoma	9 (16.1)	3 (10.3)	6 (22.2)	0.293
Contusions	24 (42.9)	11 (37.9)	13 (48.1)	0.636
Intracerebral haemorrhage	10 (17.9)	2 (6.9)	8 (29.6)	0.045

(8/94), 7.1% (4/56) and 10.5% (4/38) in the cohort with cranial CT and those without, respectively. There was no correlation between development of seizure ($p=0.913$) or obtaining of cranial CT ($p=0.230$) and mortality, rather the only predictor of mortality in this study was severity of HI ($p=0.000$).

DISCUSSION

HI poses a major health and socioeconomic problem throughout the world today.¹⁴ It affects mainly the socio-demographically productive age groups with consequent economic loss due to the cost of acute in-hospital care, rehabilitation and lost productivity. One of the significant but poorly understood sequelae of TBI is post-traumatic seizures which may occur within the first week of trauma (early) or after (late).¹ EPTS can lead to a higher incidence of mortality and morbidity due to secondary brain damage,^{2, 3} hence, low-cost and low-risk measures to reduce its incidence are desirable.

Table 3 A randomised study on the effectiveness of prophylactic phenytoin for preventing post-traumatic seizure: clinical demographics in patients who obtained cranial CT and those who did not

Variables	Cohort		P value
	with CT N=56	without CT N=38	
Age, mean (SD)	32.3 (17.5)	37.8 (17.3)	0.608
Gender, N (%)			0.054
Male	49 (87.5)	28 (73.7)	
Female	7 (12.5)	10 (26.3)	
Head injury severity, N (%)			0.65
Severe	12 (21.4)	7 (18.4)	
Moderate	8 (14.3)	12 (31.6)	
Mild	36 (64.3)	19 (50.0)	
Seizure, N (%)			0.603
Yes	7 (12.5)	4 (10.5)	
No	49 (87.5)	34 (89.5)	
Mortality, N (%)			0.594
Yes	4 (7.1)	4 (10.5)	
No	52 (92.9)	34 (89.5)	

There was a marked male preponderance of some 82%, (M:F 4.5:1) in the participants in this study as a whole. This male predominance is in accordance with various previous reports on HI both locally and from most parts of the world.^{15 16} Li *et al* in their systematic review of the global epidemiology of TBI reported male/female ratios ranging between 1.18:1 and 4.81:1.¹⁶

The age of the patients in this study ranged from 1 to 83 years (1–65 years in group A and 2–83 years in group B), with a mean age of 34.4 ± 17.5 years and a peak in the 30–49 years age group which accounted for 46.8% of the cases, (49% in group A and 44.6% in group B) (figure 1). This is in agreement with the predominance of neurotrauma in the economically productive age groups as widely reported in the literature.^{15 16} In the report by Li *et al* the average age at the time of HI ranged from 27 to 59.67 years while the median age ranged from 29 to 45 years.¹⁶ In previous studies from our country, the mean age was 29.15 years in the series by Adeleye *et al*¹⁵ while Adeolu *et al*¹⁷ reported a mean age of 26.7 ± 17.4 years. In the latter study, HI occurred most frequently at the age of 30 years. The distribution of HI in the current study showed predominance of mild HI (table 1). This predominance of mild HI is in agreement with most of the other reports in the literature.^{15 16 18} The 58.5%, 21.3% and 20.2% of mild, moderate and severe HI in this study is similar to the reported 60%, 18% and 22% of the same severity grades in the series by Adeleye *et al*,¹⁵ as in the systematic review by Li *et al*¹⁶ where the overall

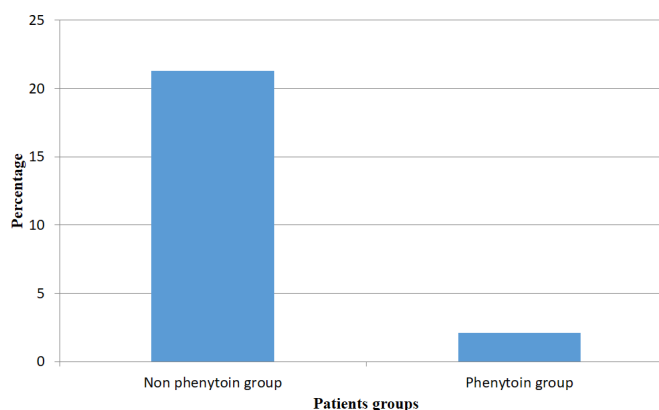


Figure 2 Incidence of seizure (in percentages) in the non-phenytoin and the phenytoin groups.

Table 4 A randomised study on the effectiveness of prophylactic phenytoin for preventing post-traumatic seizure: predictors of early post-traumatic seizure

	Seizure present	No seizure	P value
Age (years), N (%) [*]			
15 and below	6 (33.3)	12 (66.7)	0.001
Above 15	5 (6.6)	71 (93.4)	
Gender, N (%) [*]			
Male	9 (11.7)	68 (88.3)	0.993
Female	2 (11.8)	15 (88.2)	
Phenytoin prophylaxis, N (%) [*]			
None	10 (21.3)	37 (78.7)	0.008
Yes	1 (2.1)	46 (97.9)	
Severity, N (%) [*]			
Severe	5 (26.3)	14 (73.7)	0.033
Moderate	4 (20.0)	16 (80.0)	
Mild	2 (3.6)	53 (96.4)	
Contusion, N (%) [†]	5 (20.8)	19 (79.2)	0.107
Intracranial haematoma, N (%) ^{†‡}	2 (12.5)	14 (87.5)	1.000

^{*}Pearson χ^2 test performed.
[†]Fisher's exact performed.
[‡]Intracranial haematoma defined as subdural hematoma and/or intracerebral haemorrhage.

mild:moderate:severe HI ratio was 55%:27.7%:17.3% in studies that enrolled patients with all severity levels.

The overall incidence of seizure in our study was 11.7%, much higher (21.3%) in group A, the control group, than the 2.1% in group B, the treatment arm (figure 2). The overall incidence of seizure and the incidence in the phenytoin group are within the reported ranges of incidences of EPTS in the literature from other parts of the world.^{2 19-21} In comparison, however, the noted seizure incidence in the control (non-phenytoin group), is significantly higher than the previous reports on incidence of EPTS among

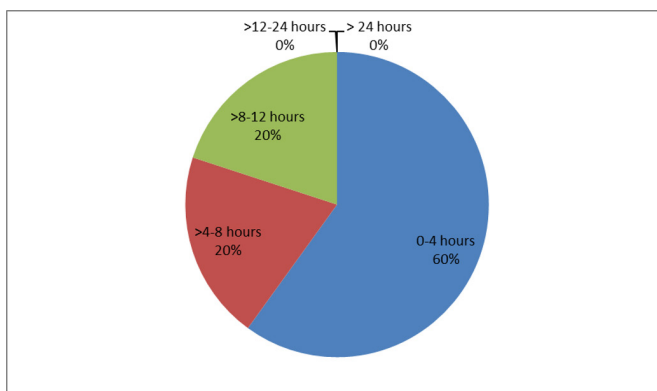


Figure 3 Timing of onset of seizure from trauma in the patients without phenytoin prophylaxis.

Table 5 Characteristics of the patients that developed seizures

Variables	Non-phenytoin group	Phenytoin group
Severity		
Mild	2 (7.4)	–
Moderate	4 (36.4)	–
Severe	4 (44.4)	1 (10.0)
Age groups		
15 and below	5 (50.0)	1 (100.0)
Above 15	5 (50.0)	–

population of patients without antiseizure prophylaxis from our environment. Odebode and Sanya²² reported an incidence of 10.2% at the University of Ilorin Teaching Hospital while Oluwole OS²³ reported an incidence of 11.9% at the University College Hospital, Ibadan. This wide variation may be due to the exclusion of patients presenting after 24 hours (which constitute a significant proportion of patients at referral hospitals like our own in this part of the world)²⁴ thereby ensuring recruitment of patients with greater risk of EPTS.

The incidence of seizure in the phenytoin group is significantly lower than the non-phenytoin group ($p < 0.01$) suggesting that a short course of phenytoin as employed in this study is effective in preventing EPTS. There is paucity of data on this phenytoin regime though. What is more, we note that the observed effectiveness of a 48-hour dose of phenytoin in this study is at variance with the reported lack of effectiveness in a strictly paediatric population by Young *et al.*²⁵ Also, the 5.9% overall incidence of EPTS in their series (7% in phenytoin group and 5% in the non-phenytoin group) was lower than this study. The authors theorised that the low seizure incidence may be due to the increased use of benzodiazepines, known antiseizure medications, in the initial management of TBI in their environment or improved ICP monitoring and control. The use of benzodiazepine in the management of HI is not a common practice in our environment and as such

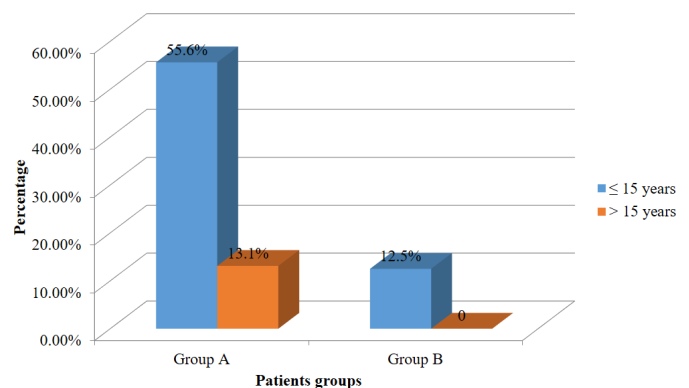


Figure 4 Percentages of patients with seizures among the paediatric and adult patients in non-phenytoin (group A) and the phenytoin (group B) groups.

may explain the higher incidence of seizure and the apparent effectiveness of a 48-hour dose of phenytoin in preventing EPTS in our study.

All seizures occurred within the first 24 hours of trauma in the control (non-phenytoin) group in our study with a mean time of onset of 4.8 hours and no episode occurring beyond 24 hours. This is in accordance with the reported peak onset of EPTS where about half to two-thirds of the cases occur in the first 24 hours.⁸ Generalised seizure predominates in our study, a finding that is similar to the study by Chan *et al* who reported similar percentages of focal and generalised EPTS (focal seizure=9.1%, generalised seizure=90.9%) as in this study.¹

The effectiveness of phenytoin in prevention of EPTS has been documented.^{15 26 27} Its administration, however, comes with attendant possible risk of complications, especially after prolonged use; and, in resource-challenged settings like our own, the additional cost of procuring the drug, and measuring the serum phenytoin levels (the former about one-third of the national minimum wage for the intravenous loading dose alone and the latter about 50%–200% of the minimum wage) is also of some economic importance. In view of the predominance of the onset of EPTS in the first 24 hours of trauma as shown in this study, and because the risk associated with short-term therapy of phenytoin are dose related and hence largely preventable, one might have to consider a 48-hour course of phenytoin prophylaxis in patients who are highly at risk of EPTS (children and patients with moderate or severe HI), particularly in resource-limited settings like our own.

Limitations

There are some limitations to the general application of the findings of this study. One, it emanated from only one institution, and the patient recruitment lasted only a very short duration of time. The rate of Cranial CT scan was rather low. And, for reasons of logistics limitations in our low-resource practice, the patients were monitored only clinically for seizure without the use of more objective screening for the presence of seizures such as static or video electroencephalography; some cases of subclinical seizures could thus be missed.

CONCLUSION

In this prospective, randomised double-blind study from a Nigerian tertiary-hospital neurosurgery practice, a 48-hour dose of phenytoin administered intravenously for prophylaxis was effective in reducing the incidence of EPTS in a cohort of patients with HI.

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Contributors TAO: conceptualisation, methodology, resources, investigation, data curation, formal analysis (lead), writing—original draft (lead), submission of the

manuscript. AAA: conceptualisation, methodology, resources, writing—review and editing (equal), validation, supervision. OAB: conceptualisation, methodology, resources, writing—review and editing (equal). JAB: conceptualisation, methodology, resources, writing—review and editing (equal). MTS: conceptualisation, methodology resources, writing—review and editing (equal). AOM: conceptualisation, methodology, resources, writing—review and editing (equal). AOA: conceptualisation, methodology, resources, writing—original draft (co-lead), review and editing (equal), validation, supervision, guarantor.

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Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

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