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The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial



The CRASH-2 collaborators*

Summary

Background The aim of the CRASH-2 trial was to assess the effects of early administration of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage. Tranexamic acid significantly reduced all-cause mortality. Because tranexamic acid is thought to exert its effect through inhibition of fibrinolysis, we undertook exploratory analyses of its effect on death due to bleeding.

Methods The CRASH-2 trial was undertaken in 274 hospitals in 40 countries. 20 211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or placebo. Patients were randomly assigned by selection of the lowest numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. We examined the effect of tranexamic acid on death due to bleeding according to time to treatment, severity of haemorrhage as assessed by systolic blood pressure, Glasgow coma score (GCS), and type of injury. All analyses were by intention to treat. The trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258, and South African Clinical Trial Register/Department of Health DOH-27-0607-1919.

Findings 10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. 1063 deaths (35%) were due to bleeding. We recorded strong evidence that the effect of tranexamic acid on death due to bleeding varied according to the time from injury to treatment (test for interaction $p < 0.0001$). Early treatment (≤ 1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5.3%] events in tranexamic acid group vs 286/3704 [7.7%] in placebo group; relative risk [RR] 0.68, 95% CI 0.57–0.82; $p < 0.0001$). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs 184/2996 [6.1%]; RR 0.79, 0.64–0.97; $p = 0.03$). Treatment given after 3 h seemed to increase the risk of death due to bleeding (144/3272 [4.4%] vs 103/3362 [3.1%]; RR 1.44, 1.12–1.84; $p = 0.004$). We recorded no evidence that the effect of tranexamic acid on death due to bleeding varied by systolic blood pressure, Glasgow coma score, or type of injury.

Interpretation Tranexamic acid should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.

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Introduction

The CRASH-2 trial showed that administration of tranexamic acid to adult trauma patients with, or at risk of, significant haemorrhage, within 8 h of injury, significantly reduces all-cause mortality (relative risk [RR] 0.91, 95% CI 0.85–0.97; $p = 0.0035$) with no apparent increase in vascular occlusive events.¹ As a consequence of this trial, tranexamic acid has been incorporated into trauma treatment protocols worldwide.

Results from the CRASH-2 trial raise some important questions. The trial was motivated by the evidence that tranexamic acid reduces bleeding in patients undergoing elective surgery, and the hypothesised mechanism was inhibition of fibrinolysis leading to improved effectiveness of haemostasis.² However, no significant

difference was recorded in transfusion requirements between the tranexamic acid and placebo groups, and the CRASH-2 trial did not measure the effect of this drug on fibrinolytic assays. Thus an alternative hypothesis is that tranexamic acid might act by reducing the pro-inflammatory effects of plasmin, rather than by improving haemostasis.³

There has also been discussion about which trauma patients should be treated with tranexamic acid. The CRASH-2 trial¹ reported the few subgroup analyses that were prespecified in the statistical analysis plan. These analyses assessed the effect of tranexamic acid on the primary endpoint of all-cause mortality, according to time since injury, systolic blood pressure, Glasgow coma score, and type of injury. No strong evidence of

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heterogeneity was recorded for any of these analyses, suggesting that tranexamic acid is likely to be equally effective in all the subgroups examined.

The focus on all-cause mortality was appropriate because it is an outcome that matters to patients and one that is not affected by the methodological problem of

competing risks.⁴ However, the effect of the trial treatment on the biologically relevant outcome could have been diluted by outcomes on which tranexamic acid might have little or no effect. In response to these concerns, we undertook exploratory analyses of the effect of tranexamic acid on mortality due to bleeding. We report the same prespecified subgroup analyses but for the outcome that we hypothesise would be most affected by this drug, specifically mortality due to bleeding.

Methods

Study design and patients

The background to the trial, methods, and baseline characteristics of the randomised patients have been previously reported.¹ Briefly, we randomly allocated 20 211 adult trauma patients with, or at risk of, significant bleeding who were within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or matching placebo, with 99.6% follow-up. In most hospitals we used a local pack system for randomisation. After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomly assigned by selection of the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The pack number was recorded on the entry form, which was sent to the Trial Coordinating Centre in London, UK. Hospitals with telephone access used a telephone randomisation service. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation.

Statistical analysis

The primary outcome was death in hospital within 4 weeks of injury, with cause of death described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, and other.

All analyses were by intention to treat. We examined the effect of the trial treatment on death due to bleeding subdivided by four baseline characteristics: (1) time from injury to treatment (≤ 1 , $>1-3$, >3 h); (2) severity of haemorrhage as assessed by systolic blood pressure (≤ 75 , $76-89$, >89 mm Hg); (3) Glasgow coma score (severe 3-8, moderate 9-12, mild 13-15); and (4) type of injury (penetrating only, blunt plus blunt and penetrating). These were the same subgroup analyses that were reported previously, but for the outcome of death due to bleeding rather than for all-cause mortality.

Heterogeneity in treatment effects across subgroups was assessed by a χ^2 test. We had prespecified that unless there was strong evidence against the null hypothesis of homogeneity of effects (ie, $p < 0.001$), the overall RR would be considered the most reliable guide to the approximate RRs in all subgroups. To test the

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20 127	0.91 (0.85-0.97); p=0.0035	0.85 (0.76-0.96); p=0.0077	0.94 (0.86-1.02); p=0.13
Time to treatment (h)				
≤ 1	7451	0.87 (0.76-0.97)	0.68 (0.57-0.82)	1.04 (0.89-1.21)
$>1-3$	6033	0.87 (0.77-0.97)	0.79 (0.64-0.97)	0.91 (0.78-1.05)
>3	6634	1.00 (0.90-1.13)	1.44 (1.12-1.84)	0.89 (0.78-1.02)
χ^2 test of homogeneity	..	4.411 (p=0.11)	23.516 (p=0.0000)	2.537 (p=0.28)

Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

	≤ 1 h (n=7451)	$>1-3$ h (n=6033)	>3 h (n=6634)
Age (years)			
Mean (SD)	33.4 (13.9)	35.0 (14.0)	35.5 (14.8)
<25	2283 (30.6%)	1557 (25.8%)	1773 (26.7%)
25-34	2360 (31.7%)	1832 (30.4%)	1882 (28.4%)
35-44	1356 (18.2%)	1177 (19.5%)	1262 (19.0%)
>44	1452 (19.5%)	1467 (24.3%)	1716 (25.9%)
Systolic blood pressure (mm Hg)			
≤ 75	1380 (18.5%)	1012 (16.8%)	768 (11.6%)
76-89	1203 (16.1%)	1064 (17.6%)	1029 (15.5%)
>89	4857 (65.2%)	3955 (65.6%)	4821 (72.7%)
Heart rate (beats per min)			
<77	681 (9.1%)	450 (7.5%)	603 (9.1%)
77-91	1189 (16.0%)	971 (16.1%)	1326 (20.0%)
92-107	1888 (25.3%)	1562 (25.9%)	1625 (24.5%)
>107	3637 (48.8%)	2990 (49.6%)	3059 (46.1%)
Respiratory rate (breaths per min)			
<10	149 (2.0%)	82 (1.4%)	77 (1.2%)
10-29	6144 (82.5%)	4992 (82.7%)	5590 (84.3%)
>29	1077 (14.5%)	901 (14.9%)	923 (13.9%)
Capillary refill time (s)			
≤ 2	2450 (32.9%)	2140 (35.5%)	2217 (33.4%)
3-4	3472 (46.6%)	2773 (46.0%)	3110 (46.9%)
>4	1131 (15.2%)	963 (16.0%)	1257 (19.0%)
Glasgow coma score			
Severe (3-8)	1000 (13.4%)	1124 (18.6%)	1494 (22.5%)
Moderate (9-12)	868 (11.7%)	915 (15.2%)	909 (13.7%)
Mild (13-15)	5577 (74.9%)	3994 (66.2%)	4214 (63.5%)
Continents			
Asia	1213 (16.3%)	2475 (41.0%)	3656 (55.1%)
Africa	2490 (33.4%)	1437 (23.8%)	872 (13.1%)
Central and South America	2453 (32.9%)	1456 (24.1%)	1355 (20.4%)
North America, Europe, and Oceania	1295 (17.4%)	665 (11.0%)	751 (11.3%)

Data are number (%), unless otherwise stated.

Table 2: Patient characteristics by time to treatment

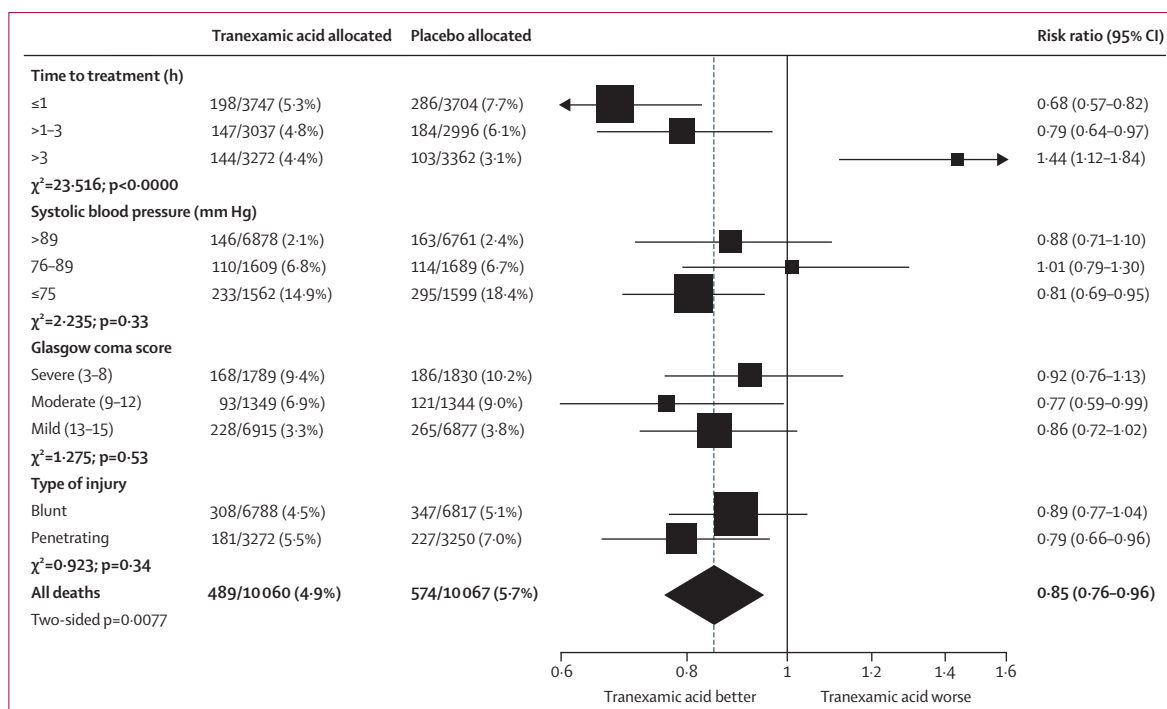


Figure 1: Mortality due to bleeding by subgroups

independence of any observed treatment interactions we ran a logistic model including all possible interactions in the four prespecified baseline characteristics and treatment subgroups.

A logistic regression was estimated with death due to bleeding as the dependent variable and treatment group and time to treatment as explanatory factors. We included an interaction parameter to allow for a proportional change in the odds ratio (OR) as time to treatment increases. ORs and 95% CIs were estimated for different times to treatment. CIs were calculated with a logistic model with time as a continuous term and an interaction term between time and tranexamic acid. We also ran a model with an interaction term for time to treatment squared to allow for a non-constant proportional change in the OR.

The trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258, and South African Clinical Trial Register/Department of Health DOH-27-0607-1919.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (IR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 3076 deaths from all causes, death due to bleeding accounted for 1063 (35%). The risk of death due to

bleeding was significantly reduced with tranexamic acid. 489 of 10060 (4.9%) patients died because of bleeding in the tranexamic acid group versus 574 of 10067 (5.7%) in the placebo group (RR 0.85, 95% CI 0.76–0.96; $p=0.0077$). We noted no significant effect on the risk of death for all other (non-bleeding) causes combined (table 1).

Table 2 shows the baseline characteristics of patients according to time to treatment. Figure 1 shows the results of the subgroup analyses for death due to bleeding. Time to treatment was unknown in nine participants. Treatment given 1 h or less from injury significantly reduced the risk of death due to bleeding (198/3747 [5.3%] in tranexamic acid group vs 286/3704 [7.7%] in placebo group; RR 0.68, 95% CI 0.57–0.82; $p<0.0001$). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs 184/2996 [6.1%]; RR 0.79, 0.64–0.97; $p=0.03$). Treatment given more than 3 h after injury significantly increased the risk of death due to bleeding (144/3272 [4.4%] vs 103/3362 [3.1%]; RR 1.44, 1.12–1.84; $p=0.004$). We recorded strong evidence that the effect of tranexamic acid on death due to bleeding varied according to time from injury to treatment ($p<0.0001$). The evidence for interaction remained strong even after adjustment for interactions between the other prespecified baseline characteristics and treatment ($p<0.0001$; data not shown).

The estimated OR of tranexamic acid on death due to bleeding when given immediately after injury was 0.61

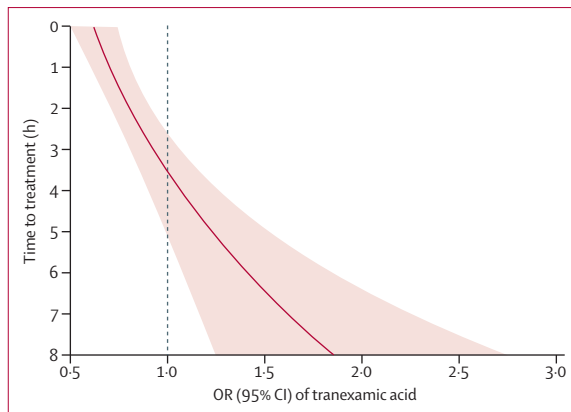


Figure 2: Effect of tranexamic acid on death due to bleeding by time to treatment

Shaded area shows 95% CI. OR=odds ratio.

(95% CI 0.50–0.74). We estimated that this OR is multiplied by 1.15 (95% CI 1.08–1.23) for every hour that passes since the injury. Figure 2 shows how the OR and 95% CIs vary with time to treatment. The interaction term for time to treatment squared was not significant (OR=0.99; $p=0.38$).

We recorded no evidence of heterogeneity for the subgroup analyses according to systolic blood pressure, Glasgow coma score at randomisation, or type of injury (figure 1). We detected no evidence of heterogeneity in the effect of tranexamic acid on the risk of non-bleeding deaths (table 1).

Discussion

The effect of tranexamic acid on death due to bleeding depends on the time between injury and onset of treatment. Early treatment with this drug seems to be much more effective than does late treatment. These results also raise the possibility that late treatment with tranexamic acid might increase the risk of death due to bleeding, although there was no evidence of any increase in all-cause mortality in patients treated after 3 h (table 1). This finding might indicate that patients treated with tranexamic acid beyond 3 h who died from bleeding might otherwise have died from some other non-bleeding cause (competing risks). If late administration does cause harm, this finding would be important since many bleeding trauma patients in low-income and middle-income countries have long prehospital times. Indeed, about a third of trauma patients in the CRASH-2 trial were treated more than 3 h after the injury.

The inclusion criteria in the CRASH-2 trial were entirely clinical, and reflect the situation that doctors are faced with in clinical practice. Patients were enrolled if the treating physician judged them to have ongoing significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage. Some of the included patients

might not have been actively bleeding. Any such misdiagnosis would have reduced the power of the trial to show an effect of tranexamic acid on mortality from bleeding, in which case the large and highly significant reduction in bleeding mortality in patients treated with this drug within 1 h of injury is particularly noteworthy.

Because patients were randomly assigned soon after hospital admission, before the precise anatomical location of bleeding and other injury was known, we were unable to do a stratified analysis based on an anatomical assessment of injury severity. We acknowledge that this omission is a methodological weakness, since such an analysis might provide insight into the mechanism of action of tranexamic acid. However, since this information would not normally be available to treating clinicians, especially in view of the importance of early treatment, the clinical value of a stratified analysis based on anatomical injury severity is small.

Data for the time between injury and treatment were available for all but nine trial participants. Because in some cases the injury would not have been witnessed, this interval sometimes had to be estimated and might therefore be inaccurate. However, any inaccuracy would be independent of the trial treatment and therefore should not bias the results. The ascertainment of a death as a bleeding death might also have been inaccurate, but similarly any inaccuracy should be independent of the trial treatment.

In clinical trials, a treatment is not often beneficial in one subgroup but harmful in another (qualitative interaction), and some trialists recommend that qualitative interactions should generally be disbelieved.⁵ The results of our analysis of the effect of tranexamic acid on death due to bleeding do, however, satisfy most of the criteria against which the credibility of subgroup results should be judged:⁶ time from injury was measured at baseline; the hypothesis that early treatment with tranexamic acid might be more effective was prespecified in the trial protocol; the interaction suggests a very low likelihood that chance explains the findings; the interaction remained significant after controlling for the non-significant interactions between treatment and the other prespecified baseline prognostic factors; the subgroup effect is large; and a biological rationale supports the interaction. Although this clinical trial was not powered to examine subgroup effects, the interaction recorded is large and highly significant.⁷

Nevertheless, we prespecified in our trial protocol that the main subgroup analyses would be undertaken for all-cause mortality, and not for mortality due to bleeding. Even though we postulated that tranexamic acid would act by reducing bleeding, we focused on all-cause mortality because overall survival is most important to patients. However, in view of the significant reduction in all-cause mortality, most of which was attributable to the effect of tranexamic acid on death due to bleeding, and the biological rationale that this drug would act by

improving haemostasis, our analyses, although not prespecified, would seem justified.

Acute severe trauma is associated with increased fibrinolysis that contributes to an early coagulopathy and increased mortality.^{8,9} Fibrinolysis can be assessed by measurement of fibrin degradation products, which include small protein fragments called D-dimers. Brohi and colleagues⁸ showed that D-dimer concentrations are raised in trauma patients at the time of hospital admission (median prehospital time 28 min), with the highest concentrations measured in the most severely injured patients.⁸ Similar results were recorded in a 2009 study from Japan that measured fibrin degradation product and D-dimers in 314 severe trauma patients.¹⁰ If this early increased fibrinolysis exacerbates bleeding and increases the risk of death, then we might expect that an antifibrinolytic drug such as tranexamic acid would be most effective in this period.

Although we had anticipated that early treatment with tranexamic acid might be most effective, the apparent increase in the risk of death due to bleeding in patients treated more than 3 h after the injury is unexpected and cannot readily be explained. It could be a chance finding and there might be no real biological effect. However, patients in the late phase of trauma can develop thrombotic disseminated intravascular coagulation, and antifibrinolytics could be contraindicated in this period.^{10,11} Although disseminated intravascular coagulation is characterised by fibrin formation and coagulation, the rapid consumption of coagulation proteins can lead to their exhaustion, resulting in uncontrolled bleeding. The need to avoid giving an antifibrinolytic in this late phase was why we restricted trial inclusion to patients who were within 8 h of injury. The possibility that the change to a prothrombotic state might occur sooner than was previously expected is open to debate and needs further research. We should also bear in mind that patients who arrive at hospital many hours after injury are likely to differ from those who arrive early. For example, there could be an increased prevalence of hypothermia and acidosis. These or other differences could explain the decreased efficacy of tranexamic acid administration when given late.

A 2011 systematic review of randomised controlled trials concluded that tranexamic acid safely reduces mortality in bleeding trauma patients.¹² Our results strongly endorse the importance of early administration of tranexamic acid in bleeding trauma patients and suggest that trauma systems should be configured to facilitate this recommendation (panel). In patients presenting late (several hours after injury) the clinician should be more cautious and make an assessment of the individual benefits and risks of this treatment, since the drug is likely to be much less effective and possibly even harmful. To the extent that our subgroup analyses are consistent with the results of studies showing an early

Panel: Research in context

Systematic review

A 2011 Cochrane systematic review¹² of antifibrinolytic drugs for acute traumatic injury identified two randomised trials of tranexamic acid in bleeding trauma patients, involving 20 451 patients. The review concluded that tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events.

Interpretation

Our results emphasise the importance of early administration of tranexamic acid and the need for caution in patients presenting several hours after the injury.

increased fibrinolytic coagulopathy, they support the hypothesis that tranexamic acid acts through the inhibition of fibrinolysis with improved haemostasis.

Future research using the CRASH-2 trial data will develop a prognostic model to predict death due to bleeding.¹³ This model will facilitate further analysis of the effect of tranexamic acid according to baseline risk of haemorrhage death.

Contributors

All members of the Writing Committee, apart from AA and GG, attended a 2-day meeting in London, UK, at which the subgroup analyses were presented and discussed and the report was drafted. Both AA and GG contributed to the discussions and drafting by phone and in correspondence.

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Conflicts of interest

Members of the Writing Committee declare that they have no conflicts of interest.

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Lampang Hospital: Surasak Meephant; Rayong Hospital: Pusit Subsompon; Roi-Et Hospital: Phaiboon Pensuan; Phrae Hospital: Wicheanrat Chamngongwit. *Tunisia* (36)—Hospital Habib Thameur: Zouheir Jerbi, Abderraouef Cherif. *UK* (135)—University Hospital of North Staffordshire: Mark Nash; Royal London Hospital: Tim Harris; Leicester Royal Infirmary: Jay Banerjee; Nottingham University Hospitals NHS Trust: Ramzi Freij; Frenchay Hospital: Jason Kendall; Countess of Chester Hospital: Stephen Moore; Hull Royal Infirmary: William Townend; Royal Sussex County Hospital: Rowland Cottingham; Derby Hospitals NHS Trust: Dan Becker; Bedford Hospital NHS Trust: Stuart Lloyd; Royal Liverpool University Hospital: Peter Burdett-Smith; Colchester General Hospital: Kazim Mirza; Royal Lancaster Infirmary: Andrew Webster; Worthing Hospital: Suzanne Brady, Amanda Groucutt; Darent Valley Hospital: John Thurston; Hope Hospital: Fiona Lecky; Northern General Hospital: Steve Goodacre. *Zambia* (62)—University Teaching Hospital, Lusaka: Yakub Mulla, Dennis Sakala; Nchanga North General Hospital: Charles Chengo.