Efficacy of aspirin and clopidogrel combined with Butylphthalide on frequent transient ischemic attack of middle-aged and elderly patients with ABCD2

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Abstract

Background: Transient ischemic attack (TIA) is the most important independent risk factor for cerebral infarction.The incidence of secondary cerebral infarction in the early stages of TIA,especially within 7 days after onset.Butylphthalide (NBP) is the only clinically approved emerging anti-ischemic drug in China,with clinical significance close to artemisinin and bicyclol.

Methods: The trial was a randomised,double-blind,controlled trial of frenquent TIA in patients aged 40 years or older from mar 1,2019 to Dec 31,2019 in Heze municipal hospital.We randomly assigned 238 patients within 24 hours after onset of TIA to both groups (loading dose of 300 mg of clopidogrel on day 1,followed by 75 mg of clopidogrel per day for 90 days,plus loading dose of 300 mg of aspirin on day 1,followed by 100 mg of aspirin per day for 90 days).In addition,the test group (NBP soft capsule 200mg three times a day for 90 days).And all patients also were divided into the low-risk layer ($ABCD^2$<4) and the medium-high-risk layer($ABCD^2$≥4) by the $ABCD^2$ scale.The primary outcome was stroke occurred(ischemia or bleeding),TIA recurrence,Acute coronary syndrome (ACS) or death on days 7 and 90.Differences in outcomes between groups were assessed by using the Cox proportional hazards model.

Results: Aspirin and clopidogrel combined with NBP was significantly better in reducing the incidence of stroke,TIA,ACS or death on the 7th and 90th days of frequent TIA than the control group (P <0.05).But in the low-risk group,the incidences of the two groups of stroke,TIA,ACS or death were lower on days 7 and 90,with no significant difference (P> 0.05).The incidence of stroke,TIA,ACS or death in the test group was significantly lower than the control group on days 7 and 90 (P <0.05).

Conclusion: In this prespecified exploratory analysis,aspirin and clopidogrel combined with NBP was superior to which aspirin and clopidogrel at preventing frenquent TIA of middle-aged and elderly patients,which is safe surely.Especially for the medium-high-risk layer with $ABCD^2$.An understanding of TIA of middle-aged and elderly patients whose mechanisms and causes is important to deliver safe and efficacious treatments for early stroke,TIA recurrence,ACS or death prevention.

Clinical Trial Registration—Chinese Clinical Trial Registry:ChiCTR2000030423.

Background

Transient ischemic attack (TIA) is the most important independent risk factor for Cerebral Infarction (CI).The incidence of secondary CI is very high in the early stages of TIA,especially within 7 days after onset,reaching 8%-10.5%[1].According to reports,the risk of stroke or Acute Coronary Syndrome (ACS) in the 3 months before the onset of TIA is 12–20%[2, 3],and the frequency TIA [4] are more likely to develop a complete stroke.Other studies have shown that TIA is not only a precursor to ischemic stroke,but also an important risk factor for Alzheimer's disease (AD) and vascular demenTIA (VD)[5],and its severity and prognosis cannot be ignored. Therefore,early detection, intervention and effective control of TIA are decisive in preventing and avoiding secondary cerebral infarction,AD and VD.Although inhibitors of platelet aggregation are formally recognized as effective drugs for TIA[6],but the etiology of TIA is complex,and the specific pathogenesis is not completely clear.It's hard control the progress of various types of TIA timely and effectively just by one category drugs.Therefore,the exploration of more effective drugs is still the focus of current research.

In the beginning,3-N-butyphthalide is a kind of biological agent originally extracted from seed of celery and NBP soft capsule is the only new drug to cure cerebral arterial thromobosis in cerebrovascular disease which was approved by China Food and Drug Administration (CFDA) in 2002.Therefore,NBP became the third original new drug with proprietary intellectual property rights in China after artemisinin and bicyclol.It was listed as one of recommended drugs in Guideline for Prevention of Cerebral Apoplexy in China in 2010 and 2014 and then NBP injection was successfully apporved to be listed in 2010 and soon became first-line drug for clinical treatment of ischemic stroke in China.

NBP,as an emerging anti-ischemic drug,inhibits platelet aggregation,reduces thrombosis,improves microcirculation,reduces cerebral infarction volume,resists oxidative stress,protects mitochondrial function,reduces neuronal apoptosis,and reduces inflammation,response and mediate autophagy of neurons,promote neurogenesis,etc in stroke animal models.It exerts multi-targeting effects on a variety of pathophysiological mechanisms and shows obvious neuroprotective effects[7–20].It has been found that its beneficial effect is far beyond the therapeutic scope of stroke[21, 22] after further research and application of its application.Especially in the field of neurodegenerative diseases,people have found that NBP and its derivatives are used in AD,VD,Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS) all have unique effects and efficacy[7, 23–25].

In addition,relevant clinical studies have shown that short-term NBP has a good clinical effect on decreasing the incidence of cerebral infarction of the patients with TIA[12].Here,we used the $ABCD^2$ scale[26] and performed a study to evaluate the efficacy and safety of the short-term Aspirin and clopidogrel combined with NBP in the treatment of frequent TIA of middle-aged and elderly patients.Thus,appropriate intervention measures should be selected for the prevention and treatment for patients with frequent TIA in different risk groups,so as to reduce the occurrence of stroke.

2. Patients And Methods

2.1 Study Design And Patients

This trial was a randomised,double-blind,controlled trial of frequent TIA of middle-aged and elderly patients from mar 1,2019 to Dec 31,2019 in Heze municipal hospital.The informed consent in written form was formally obtained from all participants,and oue study was conducted in accordance with the Declaration of Helsinki.If any patients have passed away,consent is required from the patient’s next of kin.

Eligible patients with frequent TIA[4] of middle-aged and elderly patients.Exclusion criteria:1.Head CT or MRI plain scan found intracranial hemorrhage,aneurysm or other neurological symptoms which cannot accept the treatment;2.Thrombolysis,anticoagulation therapy,carotid or cerebral or coronary artery stent implantation or reconstruction in Plan;3.Being allergic to NBP,clopidogrel and aspirin;4.A history of ventricular aneurysm,atrial fibrillation or suspected cardiovascular embolism causing TIA;5.Take in NSAIDS for more than 7 days recently;6.A history of gastrointestinal bleeding within 6 months;7.A history of a major surgery within 30 days;8.Coagulation dysfunction;9.Previous history of non-traumatic intracranial hemorrhage;10.Severe liver and kidney dysfunction;11.Pregnancy or lactation;12.Incomprehension or incooperation with the study or treatment or follow-up.Additionally,standard treatments such as hypoglycemic and antihypertensive therapy may be prescribed to all patients at the discretion of the investigators and clinicians.

2.2 Randomization And Treatments

Patients enrolled were randomly assigned to 1 of the 2 treatment groups with the use of a double-blind,double-dummy design.The site investigator called into an automated system that randomly assigned a number corresponding to a medication kit stored at the research site,and the medication in the kit was administered to the patient.NBP soft capsule and the matching placebo were purchased from Shijiazhuang Pharmaceutical Group Co.Ltd,which had no other role in the study.We randomly assigned 238 patients within 24 hours after onset of TIA to test group (loading dose of 300 mg of clopidogrel on day 1,followed by 75 mg of clopidogrel per day for 90 days,plus loading dose of 300 mg of aspirin on day 1,followed by 100 mg of aspirin per day for 90 days;NBP soft capsule 200 mg three times a day for 90 days) or control group (loading dose of 300 mg of clopidogrel on day 1,followed by 75 mg of clopidogrel per day for 90 days,plus loading dose of 300 mg of aspirin on day 1,followed by 100 mg of aspirin per day for 90 days;NBP soft capsule placebo 200 mg three times a day for 90 days).After day 90,treatment was at the choice of the clinician and the patient.

Additionally,standard treatments such as hypoglycemic and antihypertensive therapy may be prescribed to all patients at the discretion of the investigators and clinicians.Previous studies[27] indicated that 90% of strokes occurred in the layer with $ABCD^2 \geq 4$,so all the patients were divided into the low-risk layer (85,39.7%) and the medium-high-risk layer (129,60.3%) by the $ABCD^2$ scale.

All patients ought to return to hospital or keep in contact with the researchers by telephone on days 7 and 90 for follow-up,and the occurrence of possible outcome events,changes of test drugs and possible adverse events should be recorded.

2.3 Outcome Criteria

Patients were evaluated clinically or followed up on days 7 and 90.The endpoint of the trial was a compound event of Stroke,TIA,ACS or death (death from cerebrovascular disease) on days 7 and 90,which conforms to a standard definition[28],or the occurrence of serious or uncoordinated non-serious adverse events[29].

2.4 Statistical Methods

All data were analyzed by using SPSS 22.0 (SPSS Inc,Chicago,IL) software and tabulated using Microsoft office software (word,excel).All data were expressed as the mean standard deviation (SD).Differences in baseline factors (age,sex,concomitant medications,risk factors) among the groups in the different layers were compared using the T-test or chi-square test.COX regression analysis on the influence factors for resolving time of the two groups in all patients and the different layers.The treatment effects were compared with analysis of variance and 95% confidence intervals (CIs).Statistical analysis of safety data was done with Pearson chi-square test.$P < 0.05$ was regarded significant difference.

3. Conclusion

3.1 patient characteristics

The baseline characteristics of the patients in this study are shown in Table 1.In all 228 patients with frequent TIA,14 patients who quit in process,and the remaining 214 patients completed the study smoothly.There was 90 (42.1%) patients were female and there were no significant difference in age,sex,risk factors or concomitant medication.The greatest risk factors for these two groups were smoking (test group:54.1%;control group:49.5%),hypertension (Test group:48.6%;Control group:51.5%),and hypercholesterolemia (Test group:55.0%;Control group:48.5%).There was no significant difference in these risk features.Similarly,there was also no significant difference in these risk features in the low-risk layer and the medium-high-risk layer by the $ABCD^2$ scale.There was only one death in each of the two groups,and COX regression analysis the resolving time of the two groups was also no significant difference ($P > 0.05$).

3.2 Curative Effect Results

3.2.1 Follow-up results of all patients ($ABCD^2 = 0–7$) on the 7th and 90th day after treatment

As shown in Table 2,on the 7th day of treatment,there were 2 cases (1.8%) of stroke,TIA,ACS or death in the test group and 12 cases (11.7%) in the control group.On the 90th day of treatment,there were 8 cases (7.2%) of stroke,TIA,ACS or death in the test group and 20 cases (19.4%) in the control group.The incidence of stroke,TIA,ACS or death in the test group was significantly lower than that in the control group on the 7th and 90th day of treatment,all showed obvious difference ($P < 0.05$).

3.2.2 Follow-up results of Low-risk group (ABCD ^{2} < 4) on the 7th and 90th day after treatment

As shown in Table 2,there were 45 cases in the test group and 40 cases in the control group.On the 7th day of treatment,1 (2.2%) case of total cases of stroke,TIA,ACS or death occurred in the test group;and 3 (7.5%)cases in the control group.Treatment follow-up on the 90th day showed that 2 (4.4%) cases of stroke,TIA,ACS or death occurred in the test group and 5 (12.5%) cases in the control group.The incidence of stroke,TIA,ACS or death were lower in the two groups on the 7th and 90th days of treatment. showed no significant difference in efficacy (P > 0.05).

3.2.3 Follow-up results of the medium and high-risk group (ABCD ^{2} ≥ 4) on the 7th and 90th day after treatment

As shown in Table 2,there were 66 cases in the test group and 63 cases in the control group.On the 7th day of treatment,2 (3.0%) cases of stroke,TIA,ACS or death occurred in the test group;and 9 (14.3%) cases in the control group;follow-up after 90 days of treatment,it was found that 6 (9.1%) cases of stroke,TIA,ACS or death occurred in the test group and 15 (23.8%) cases in the control group.No matter on the 7th or 90th day of treatment,the incidence of stroke,TIA,ACS or death in the test group was significantly lower than that in the control group,and the efficacy was significantly different (P < 0.05).

3.3. Safety Results

As shown in Table 2,1(0.9%) case with subcutaneous bleeding,4 (3.6%) cases with nasal and gum bleeding in the test group;and 3 (2.9%) cases with subcutaneous bleeding,2 (1.9%) cases with nasal and gum bleeding in the control group.However,there was no significant difference in the incidence of bleeding between the two groups.No primary intracranial hemorrhage or gastrointestinal hemorrhage was observed in either groups.

4. Discussion

The purpose of this study was to evaluate the efficacy and safety of the 90-day NBP in the treatment of patients with frequent TIA.First of all,we discuss the specific performance of two groups under the low- risk and medium-high-risk layers with ABCD^2 scale.

Table 2 showed that on the 7th and 90th day of treatment,no matter which plan was used,the disease progression can be well controlled in the low-risk group.It might be that the low-risk group had a lower risk of stroke,TIA,ACS or death,which was easier to control.

Table 2 showed that on the 7th and 90th day of treatment,the incidence of stroke,TIA,ACS or death in the test group was significantly lower than that in the control group,indicating that the efficacy of Aspirin and clopidogrel combined with NBP in the treatment of frequent TIA in the medium-high-risk group was more accurate than that in the double antibody group

In this study,all patients with frequent TIA at 90 days' NBP treatment were more effective than the 90 days' dual antibody plan.This might be due to the proportion of patients (129,60.3%) with ABCD^2 ≥ 4 in the study population was large,thus the overall distribution,and the results showed the larger proportion of the medium-high-risk group of the results.

NBP as a new type of anti-ischemic drug, its active ingredient is mainly dl-3-N-butylphthalide.Its mechanism of action on TIA may be related to its unique pharmacological effect [30–35]:1.Up-regulate cAMP levels and inhibit 5 -HT releases,blocks the p2y1 receptor to the cGMP-NO signaling pathway,and inhibits cytoplasmic plaque-mediated TXA 2 synthesis[36–38],thereby inhibiting platelet aggregation and reducing thrombosis.2.Increases prostaglandin I2(PGI2)/T ranexamic acid 2 ratio,reverse microvascular spasm,improve cerebral blood flow,and then restore damaged microcirculation[39].3.Upregulate FGF-2 expression,activate ERK1/2 and PI3K/akt-endothelial cells NOS signaling pathway[40],regulates VEGF and hypoxia-induced factor-1α (HIF-1α) brain microangiogenesis,prevents hypothermic response to ischemic stroke[41, 42].4.NBP can enhance neuronal mitochondrial Na^+/K^+-atp enzyme,Ca^+-atp enzyme and respiratory chain complex activity[43];improve mitochondrial

morphology after ischemia,maintain mitochondrial membrane fluidity,protect mitochondrial mitochondrial potenTIAl;significantly increase ischemic damage Post-stroke ATP levels,reduce lactic acid release,and restore ion homeostasis,thereby reducing cerebral edema[44].5.NBP can inhibit mitochondria after strokeRelease of cytochrome c and apoptosis-inducing factor (AIF),thereby inhibiting a series of apoptosis-associated proteins[45, 46] that are caspase-dependent and non-caspase-dependent;it can also significantly block ischemia by inhibiting the activation of JNK Reperfusion-induced neuronal apoptosis.6.NBP can inhibit the Nogo-A/NgR and RhoA/ROCK signaling pathways[47],promote axons, synapse formation and nerve regeneration in the subventricular region after stroke;up-regulate ischemic Potassium channel TREK-1 (TWIK-re-lated K^+channel 1,TREK-1) in the biporous region after stroke,which affects the proliferation of neural stem cells and astrocytes[48–51];significantly promotes hippocampus after stroke Cell proliferation,increase the survival rate of newborn cells,and regulate the differenTIAtion of newborn cells to mature neurons.7.NBP can significantly increase mitochondrial SOD and glutathione peroxidase (GSH-Px) activities and reduce mitochondrial malondialdehyde (MDA) Level[52]; regulates the induction of NOS mRNA levels and inhibits NF-κB activation,protecting neurons from oxidative stress.8.NBP can prevent neutrophil infiltration and reduce intercellular expression after ischemic injury adhesion of molecule-1 (ICAM-1) and TNF-α[53];can also inhibit the expression of IL-6 and IL-1 and enhance liverCell growth factor (HGF),and inhibiting the expression of NF-κB signaling pathway,reduce the activation of astrocytes[54],thereby reducing inflammation,reducing damage after ischemic injury.

Previous studies[16, 55]have found that the changes of ALT and AST induced by NBP were not significantly different from those in the control group,thus monitoring on serum Alanine transaminase (ALT) and Aspartate transaminase (AST) levels wasn't included in this study.Table 2 in this study showed that the incidence of adverse events was similar and the difference was not statistically significant.This finding suggested that NBP was safe for patients with frequent TIA.

Conclusion

An understanding of frequent TIA of middle-aged and elderly patients whose mechanisms and causes is important to deliver safe and efficacious treatments for early stroke,TIA recurrence,ACS or death prevention.In this prespecified exploratory analysis,our results indicated that the long-term and continuous aspirin and clopidogrel combined with NBP was superior to which aspirin combined with clopidogrel at preventing frequent TIA of middle-aged and elderly patients,which is safe surely.Especially for the medium-high-risk layer with $ABCD^2$.Our study is a newly finished,and requires further inspection,verification and improvement,so there is need to carefully interpret the results.Although the distribution of baseline factors that can affect functional outcomes in this study are similar,there is no significant difference.And due to the relatively small sample size,so multi-center and large-sample trials are urgently needed to further confirm that long-term NBP treatment of frequent TIA of middle-aged and elderly patients is effective and reliable without significant side effect.We all look forward to NBP,which is from China and is used like artemisinin Drugs that serve the world can have broader prospects.

Abbreviations

NBP=N-Butylphthalide;TIA=Transient ischemic attack;CI=Cerebral infarction;ACS=Acute coronary syndrome; AD=Alzheimer's disease;VD=vascular demen;CFDA=China Food and Drug Administration;PD=Parkinson's disease;ALS=Amyotrophic Lateral Sclerosis.ALT=Alanine transaminase;AST=Aspartate transaminase.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Heze municipal hospital reviewed and approved the purpose and design of our work.Informed consent in written or oral form was formally obtained from all participants,and our was conducted in

accordance with the Declaration of Helsinki.If any patients have passed away,consent was required from the patient's next of kin.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

QW and HL carried out the experimental work and the data collection and interpretation.YW participated in the design and coordination of experimental work, and acquisition of data.HZ and YG participated in the study design,data collection,analysis of data and preparation of the manuscript.YC carried out the study design,the analysis and interpretation of data and drafted the manuscript.All authors read and approved the final manuscript.

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Tables

Table 1
Baseline characteristics.

Characteristic	$ABCD^2$=(0-7)				$ABCD^2$ <4				$ABCD^2$≥4			
	Test Group N=122(%)	Control Group N=99(%)	Hazard Ratio(95% CI)	P Value	Test Group N=50(%)	Control Group N=42(%)	Hazard Ratio(95% CI)	P Value	Test Group N=72(%)	Control Group N=57(%)	Hazard Ratio(95% CI)	P Value
Demographic characteristics	111	103			45	40			66	63		
Age, y												
Median	61.14	60.25	-3.602-1.832	0.521	56.47	56.00	-4.751-3.818	0.829	64.32	62.97	-4.516-1.814	0.400
Range	40-80	40-80			40-80	40-80			40-80	40-80		
Female, n (%)	48(43.2%)	42(40.8%)	0.904(0.525-1.556)	0.782	24(533%)	25(62.5%)	0.686(0.288-1.633)	0.510	27(40.9%)	27(42.9%)	1.083(0.538-2.181)	0.860
Selected clinical characteristics												
Current/previous smoking	60(54.1%)	51(49.5%)	1.200(0.701-2.053)	0.584	21(46.7%)	12(30.0%)	2.042(0.835-4.995)	0.126	39(59.1%)	39(61.9%)	0.889(0.438-1.802)	0.857
Hypertension	54(48.6%)	53(51.5%)	0.894(0.523-1.528)	0.784	9(20.0%)	14(35.0%)	0.464(0.175-1.234)	0.146	45(68.2%)	39(61.9%)	1.319(0.638-2.725)	0.467
Hypercholesterolemia	61(55.0%)	50(48.5%)	1.293(0.755-2.214)	0.412	10(22.2%)	6(15.0%)	1.619(0.530-4.946)	0.422	51(77.3%)	44(69.8%)	1.468(0.668-3.228)	0.425
Diabetes	30(27.0%)	24(23.3%)	1.219(0.656-2.266)	0.637	7(15.6%)	5(12.5%)	0.289(0.375-4.439)	0.762	23(34.8%)	19(30.2%)	1.239(0.592-2.593)	0.580
Coronary heart disease	26(23.4%)	21 (20.4%)	1.194(0.623-2.288)	0.623	3(6.7%)	6 (15.0%)	0.405(0.094-1.739)	0.295	23(34.8%)	15 (23.8%)	1.712(0.793-3.696)	0.182
Concomitant medications												
Nitrates	26(23.4%)	21 (20.4%)	1.194(0.623-2.288)	0.623	3(6.7%)	6 (15.0%)	0.405(0.094-1.739)	0.295	23(34.8%)	15 (23.8%)	1.712(0.793-3.696)	0.182
Antihypertensive agents												
Diuretics	28(25.2%)	19(18.4%)	1.491(0.773-2.876)	0.251	4(8.9%)	2 (5.0%)	1.854(0.321-10.708)	0.679	24(36.4%)	17(27.0%)	1.546(0.731-3.270)	0.264
Beta-blockers	26(23.4%)	20 (19.4%)	1.269(0.658-2.448	0.509	3(6.7%)	5(12.5%)	0.500(0.112-2.241)	0.466	23(34.8%)	15 (23.8%)	1.712(0.793-3.696)	0.182
Calcium antagonists	39(35.1%)	41(39.8%)	0.819(0.470-1.426)	0.572	10(22.2%)	10(25.0%)	0.857(0.314-2.337)	0.802	29(43.9%)	31(49.2%)	0.809(0.405-1.618)	0.599
Angiotensin II receptor blockers	17(15.3%)	21(20.4%)	0.706(0.349-1.429)	0.373	1 (2.2%)	4(10.0%)	0.205(0.022-1.912)	0.183	16 (24.2%)	17(27.0%)	0.866(0.392-1.911)	0.840
Angiotensin-converting enzyme inhibitors	28(25.2%)	19(18.4%)	1.491(0.773-2.876)	0.251	8(17.8%)	5(12.5%)	1.514(0.452-5.571)	0.559	20(30.3%)	14(22.2%)	1.522(0.689-3.362)	0.324
Lipid-lowering drugs												
Fibrates	21(18.9%)	17(16.5%)	1.180(0.584-2.388)	0.722	4(8.9%)	5(12.5%)	0.683(0.170-2.742)	0.729	17(25.8%)	12(19.0%)	1.474(0.639-3.404)	0.404
Nicotinic acid	28(25.2%)	23(22.3%)	1.173(0.624-2.206)	0.634	4(8.9%)	2(5.0%)	1.854(0.321-10.708	0.679	24(36.4%)	21(33.3%)	1.143(0.553-2.360)	0.854
Statins	60(54.1%)	45(43.1%)	1.516(0.884-2.600)	0.135	11(24.4%)	7(17.5%)	1.525(0.527-4.410)	0.596	49(50.9%)	38(50.6%)	1.896(0.898-4.005)	0.132
Antidiabetic drugs												
oral hypoglycemic agents	26(23.4%)	17(16.5%)	1.547(0.783-3.057)	0.234	6(13.3%)	2(5.0%)	2.923(0.555-15.396)	0.272	20(30.3%)	15 (23.8%)	1.391(0.636-3.042)	0.435
Insulin	21(18.9%)	12(11.7%)	1.769(0.822-3.809)	0.185	6(13.3%)	3(7.5%)	1.897(0.442-8.146)	0.491	15(22.7%)	9(14.3%)	1.765(0.710-4.387)	0.261

Table 2
Outcome

	Test Group N (%)	Control Group N (%)	Hazard Ratio(95% CI)	P
$ABCD^2$=(0-7)	111	103		
The 7th day of treatment	3(2.7)	12(11.7)	4.747(1.300–17.341)	0.014<0.05
The 90th day of treatment	8(7.2)	20(19.4)	3.102(1.301–7.401)	0.009<0.05
$ABCD^2$ <4	45	40		
The 7th day of treatment	1(2.2)	3(7.5)	3.568(0.356–35.762)	0.338
The 90th day of treatment	2(4.4)	5(12.5)	3.071(0.561–16.804)	0.246
$ABCD^2$≥4	66	63		
The 7th day of treatment	2(3.0)	9(14.3)	5.333(1.105–25.748)	0.028<0.05
The 90th day of treatment	6(9.1)	15(23.8)	3.125(1.127–8.666)	0.031<0.05
Safety outcomes[30] of $ABCD^2$=(0-7)				
Primary intracranial hemorrhage	0	0		
Subcutaneous hemorrhage	1(0.9)	3(2.9)	0. 031(0.031–2.961)	0.354
Nasal and gum bleeding	4(3.6)	2(1.9)	1.888(0.338–10.532)	0.684
Gastrointestinal hemorrhage	0	0		

Figures

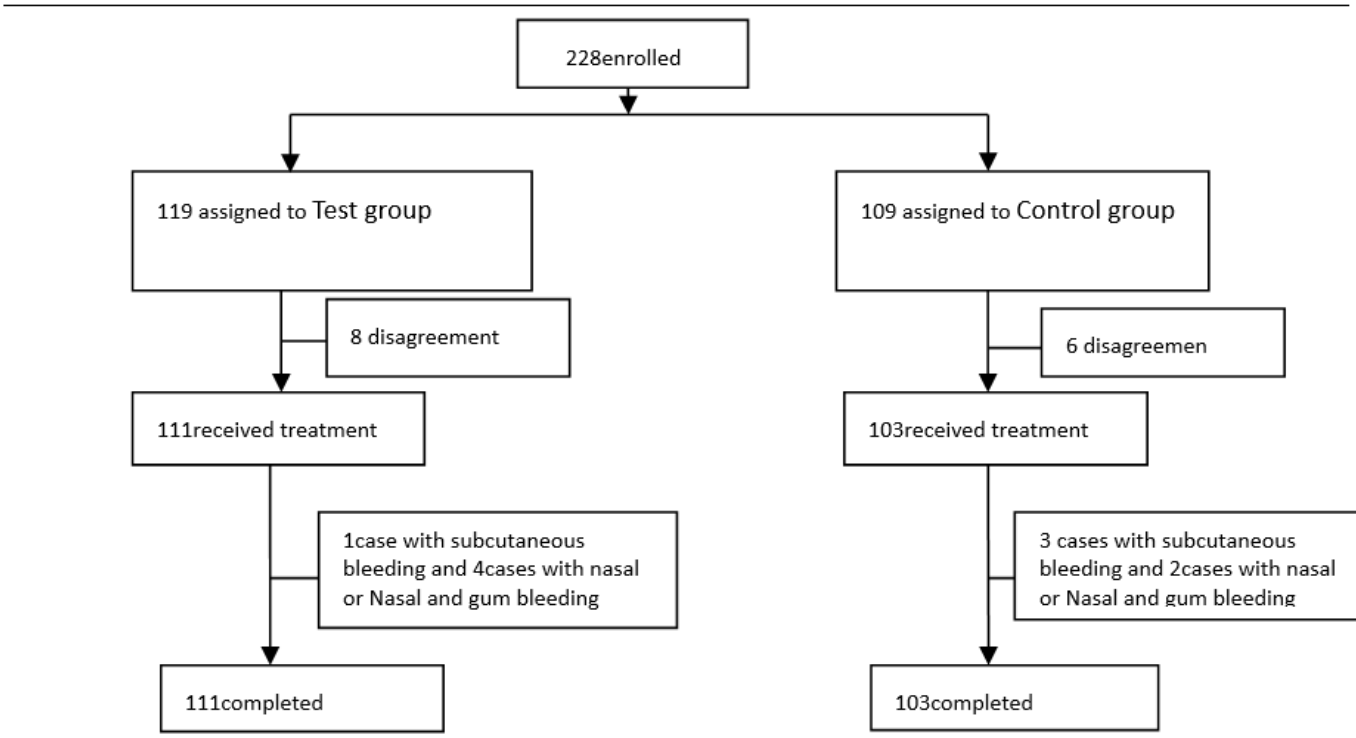

Figure 1. profile of the clinicle trial

These patients with side effects recovered by themselves and needed no additional medications.

Figure 1

Profile of the clinicle trial