**ADIGRAT UNIVERSITY**

**COLLEGE OF MEDICINE AND HEALTH SCIENCES**

**DEPARTMENT OF PHARMACY**



**Drug Informatics Individual Assignment On;**

A Critical Appraisal Endovascular Therapy After Intravenous t-PA Versus t-PA Alone for Stroke

**Prepared by:**- Selamawit Mengstu

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**Over view of the study**

* Endovascular therapy is increasingly used after the administration of intravenous tissue plasminogen activator (t-PA) for patients with moderate-to-severe acute ischemic stroke, but whether a combined approach is more effective than intravenous t-PA alone is uncertain.
* The study was planned to enroll a maximum of 900 participants, 18 to 82 years of age, at 58 centers.
* The study was stopped early because of futility after 656 participants had undergone randomization (434 patients to endovascular therapy and 222 to intravenous t-PA alone).
* Randomly assigned eligible patients who had received intravenous t-PA within 3 hours after symptom onset to receive additional endovascular therapy or intravenous t-PA alone, in a 2:1 ratio.
* All participants began receiving a standard dose of intravenous t-PA (0.9 mg per kilogram), with 10% as a bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg). Throughout the trial, randomization was required within 40 minutes after the initiation of the infusion.
* Participants randomly assigned to the endovascular-therapy group underwent angiography as soon as possible. Participants who had no angiographic evidence of a treatable occlusion received no additional treatment.
* There was no significant difference between the endovasculartherapy and intravenous t-PA groups in the overall proportion of participants with a Rankin score of 2 or less (40.8% and 38.7%, respectively). Significant difference in the predefined subgroups of patients with an NIHSS score of 20 or more indicating severe stroke. patients with a score of 8 to 19, indicating moderately severe stroke.
* The trial showed similar safety outcomes and no significant difference in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone.

***Background***

***Credibility of the journal and authors***

* Publisher NEJM is one of the finest and oldest medical journals on 1812
* Profile of the authors MPHs, MDs, PhDs
* All of them contribute their role in research.

***Title And Summary Of The Study***

* The title well explained the research body.
* This study try to assess Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke.
* Endovascular therapy is increasingly used after the administration of intravenous tissue plasminogen activator (t-PA) for patients with moderate-to-severe acute ischemic stroke.

***The Abstract***

* The abstract provide a very concise overview or summary of the research which, includes the background, objective, methodology, result and conclusion of the study.
* It does identified the research problem in its background.
* ***However,*** the number of the study participant was mentioned in the result part of the abstract, instead it should mentioned in the method part of the abstract and also the conclusion was shortly indeed.

***Introduction***

***Purpose of the study***

* It is an important study since intravenous tissue plasminogen activator (t-PA; alteplase is the only proven reperfusion therapy for acute ischemic stroke but its clinical effectiveness is critically time-dependent and have limitation of dependence on available serum plasminogen.
* Associating the importance of Endovascular therapy for acute ischemic stroke it recanalizes occlusions in large arteries more frequently and rapidly than intravenous t-PA and is increasingly used to treat patients with occlusions of the large intracranial arteries in institutions with the required expertise.
* ***However,***the introduction didn’t clearly state the aim of the research at the end of the introduction part.

***Statement Of The Problem***

* The research question of this study is clearly identified.
* Few patients with ischemic stroke (10%) meet current eligibility criteria for the use of intravenous t-PA, including arrival within a relatively short therapeutic time window (4.5 hours) after symptom onset. Limitations of intravenous t-PA include dependence on available serum plasminogen, the resistance of an old or large thrombus to fibrinolysis, and the risks of systemic and cerebral hemorrhage.

***The literature review***

* The research over viewed the outcome of Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke.
* It is highly relevant to this research which mainly focused on the Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke on its its primary and secondary outcomes.
* ***However,*** it comes by evidence of with the earliest date is conducted in 1960 and the latest review is by 2012.

***Funding Sources***

* Supported by grants from the National Institutes of Health and the National Institute of Neurological Disorders and Stroke (UC U01NS052220, MUSC U01NS054630, and U01NS077304) and by Genentech, EKOS, Concentric Medical.
* This shows the study have good importance for the community.
* Cordis Neurovascular and Boehringer Ingelheim were not participated in any activity of the study.

***Methodology***

***Study design***

* Its good to use a phase 3, randomized, open-label clinical trial with a blinded outcome.
* All participants receive a standard dose of intravenous t-PA (0.9 mg per kilogram), with 10% as a bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg). Randomization was required within 40 minutes after the initiation of the infusion.
* Allocate of the treatment was very good as they randomly assigned to the intravenous t-PA group received the remainder of the standard dose and randomly assigned to the endovascular therapy group underwent angiography as soon as possible with intravenous t-PA.

***Sample size, sampling method, study period and eligibility of the participants***

* The researchers had a clearly-identified target population and study period:
* which was 58 study centers between August 25, 2006, and April 17, 2012 in the United States (41 sites), Canada (7), Australia (4), and Europe (6).
* Besides, they had clearly list of inclusion and exclusion criteria to group participants:
* Eligibility criteria included receipt of intravenous t-PA within 3 hours after symptom onset and a moderate-to-severe neurologic deficit (defined as an NIHSS score ≥10 or, after approval of amendment 3, a score of 8 to 9 with CT angiographic evidence of an occlusion of the first segment of the middle cerebral artery [M1], internal carotid artery, or basilar artery at institutions where CT angiographic imaging at baseline was the standard of care for patients with acute stroke).
* ***However,*** the sampling method of this research is not clearly specified. Simply stated a total of 656 participants underwent randomization (434 participants to endovascular therapy and 222 to intravenous t-PA alone).

***Data Collection, Analysis And Ethical Consideration***

* This study well thought-out about the patients’ ethics because it clearly stated as a trial protocol, which is available at (NEJM. Org):
* Written informed consent was obtained from the patient or a legal representative before enrollment.
* Disclosure forms provided by the authors are available with the full text.
* The design, analysis, and data collection for the IMS III trial, as well as the writing of the manuscript, were performed by members of the executive committee and investigators at the study sites.
* These investigators vouch for the accuracy and completeness of the presented data and for the fidelity of this report to the study protocol

***However,*** *t*he trial was stopped early because of futility,according to the prespecified rule this may lead to loss to follow up during the study period.

***Findings/Results Of The Study***

* The results of the study were presented in a suitable manner.
* The main result stated clearly as primary and secondary outcomes:
* There was no significant difference between the endovascular therapy and intravenous t-PA groups in the overall proportion of participants with a modified Rankin score of 2 or less (40.8% and 38.7%, respectively. NIHSS score of 20 or more, indicating severe stroke (difference of 6.8 percentage points in favor of the endovascular-therapy group and patients with a score of 8 to 19, indicating moderately severe stroke (difference of 1.0 percentage point in favor of the intravenous t-PA group as primary out come.
* Predefined secondary analyses showed no significant differences among the subgroups.
* Again, the result of this study had been highlighted and clearly presented coherently through tables and graphs.
* ***However,*** the result shows that they did not find a significant benefit of endovascular therapy in patients with severe stroke.

***Analysis/Discussion***

* The discussion of this study is balanced with its analysis.
* It clearly refer back to points raised in the introduction:
* Although an earlier time to endovascular therapy was hypothesized to be associated with greater benefit, the results of relevant prespecified subgroup analyses were not significant.
* The limitation and the strength of study clearly stated:
* one limitation of trial is that it did not compare the efficacy of the new stent retrievers with that of intravenous t-PA alone. However, the study highlights the finding that improved reperfusion is not a guarantee of clinical efficacy.
* Finally, the discussion consistently relates the key findings to research's discussed earlier.

***Conclusion And Recommendation***

* This research didn’t sums up as good as possible since they show the study’s whole content and what was most useful and interesting about the research they simply said:
* The IMS III trial of endovascular therapy for acute ischemic stroke address the promise and limitations of endovascular therapy.
* The study clearly stated a recommendation the ways in which current research could be improved:
* The use of randomization in ongoing and future stroke trials, rather than the treatment of eligible patients with endovascular therapy outside any trial, and minimization of the time to treatment will be essential for assessing the potential benefit of endovascular therapy for acute ischemic stroke.
* Besides, the gap in the research were summarized and outline the implication of the study for further researches.
* Generally, this study is very relevant to health professionals and as a large input to the pharmacy profession specifically.

***Reference They Used***

* It is Vancouver method of referencing which is most common in a myriad of publications and got an acceptability from most publisher institutions.

***Is it PICO?***

* This research give attention to PICO under consideration as
* A **Problem** of intravenous t-PA include dependence on available serum plasminogen, the resistance of an old or large thrombus to fibrinolysis, and the risks of systemic and cerebral hemorrhage.
* Appropriate and clearly stated treatment strategy (**Intervention**) and
* A suitable control or alternative **Comparison** between Endovascular Therapy after t-PA vs. t-PA Alone.
* But, the desired results or patient related consequences haven’t been identified (**Outcomes**)
* Simply they said the IMS III trial of endovascular therapy for acute ischemic stroke address the promise and limitations of endovascular therapy.