PUBLICATION ALERT NEWSLETTER

Please be aware that the purpose of this Newsletter is to make you familiar with the most recent scientific publications, and you must keep in mind that all aspects may not be covered by the label. Please always refer to the current prescribing information as in force in your country.

Medicine is an ever-changing field. Progress may not always be rapid, but our understanding of disease improves, new treatments emerge, and systems of care need to be adapted accordingly. Processes need to be developed or refined to ensure that patients receive the best standard of care and have the greatest chance of optimal outcomes.

An example of this is the developing field of reperfusion therapies in acute ischaemic stroke (AIS). In addition to intravenous (IV) recombinant tissue plasminogen activator (rt-PA), endovascular therapy (EVT) has become a critical component of stroke care, particularly for large vessel occlusion (LVO) strokes. Because several teams are looking at the potential of removing the lytic from their reperfusion strategies and opting only for mechanical thrombectomy (MT), it is of importance to remind them that the Guidelines clearly confirm that the combination of both approaches is key for patients with LVO.

In this issue of the Actilyse® Publication Alert Newsletter, we look at an article that tries to evaluate the percentage of LVOs (because there is no common definition of LVO, and rarely an accurate calculation of the number of patients involved); we also feature a review article that looks at how prehospital assessment of patients with acute stroke will need to evolve in order to best identify LVO stroke and treat the patient accordingly, and we report on a study of MT in a critical care unit. Another topic of growing interest is the comparison between lytics. Here we detail the outcomes of an *in vitro* study comparing the thrombolytic efficacy of tenecteplase (TNK) and rt-PA.

ESTIMATES OF THE PREVALENCE OF LARGE VESSEL OCCLUSION STROKE VARY CONSIDERABLY IN THEIR METHODS

To determine the systems and resources required for stroke care, an accurate estimation of the prevalence of LVO stroke is important. A systematic review by Waqas *et al*. aimed to estimate the prevalence of LVO among patients with AIS, with emphasis on the definitions and methods used by different studies.[1]

Eighteen studies were included in the analysis, and the reported prevalence of LVO among patients with AIS ranged from 13% to 52%. There was significant heterogeneity among the studies.

The AIS denominator from which LVO rates were derived was not consistent. This is important when comparing LVO estimates between studies because they all report LVO prevalence as a percentage of a larger AIS cohort, which was determined differently from study to study. The authors of the review calculated that the pooled prevalence of LVO was 30% (95% confidence interval [CI]: 25–35) among patients with confirmed AIS and 21% (95% CI: 19–30) among patients with suspected AIS. The method of determining the AIS denominator significantly influenced heterogeneity.

In addition, nine different definitions of LVO were used across the studies, based on occlusion site, and the methods used for estimating LVO also varied (e.g. retrospective vs prospective, population-based vs single hospital experience).

Overall, the review highlights the heterogeneity of the existing literature regarding the prevalence of LVO. The authors call for studies with a uniform definition of LVO and methods of estimation of AIS in order to provide an estimate of the true prevalence of LVO among patients with AIS.

Study details

- Systematic review of articles reporting the prevalence of LVO based on computed tomography (CT) angiography or magnetic resonance (MR) angiography findings in a population-based or hospital-based setting that were published between 1 January 2000 and 30 June 2018, irrespective of the method of determining LVO
  - Studies without consecutive recruitment or without confirmation of LVO with CT angiography or MR angiography were excluded. Articles in languages other than English were excluded
- Eighteen records met the criteria for inclusion. Five studies presented population-based estimates. Eight studies were retrospective, with data derived from hospital databases or registries. Five studies were prospective investigations of consecutive patients presenting with ischaemic stroke
- Across the studies, the reported prevalence of LVO ranged from 13% to 52%
- There was significant heterogeneity among the included studies (I^2 = 99%; p<0.001)

- The AIS denominator, the definition of LVO, and the methods used for estimating LVO prevalence all varied between studies. The method of AIS denominator determination significantly influenced heterogeneity (p=0.018)
- Random effects models found that the pooled prevalence of LVO was:
  - 21% (95% CI: 19–30) among patients with suspected AIS
  - 30% (95% CI: 25–35) among patients with confirmed AIS
- Based on eight studies, the pooled estimate of LVO prevalence in the USA was 28.8% (95% CI: 21.2–36.5). Based on ten studies, the pooled estimate of LVO prevalence outside the USA (UK, Australia, Netherlands, Switzerland, France, Denmark, Chile) was 29.3% (95% CI: 22.0–37.0)

"Studies with a standardized LVO definition and methods of AIS estimation are necessary to estimate the true prevalence of LVO among patients with AIS"[1]

SYSTEMS OF CARE MUST ENSURE ACCURATE PREHOSPITAL ASSESSMENT AND TRIAGE OF PATIENTS WITH LARGE VESSEL OCCLUSION STROKE

EVT may be a more effective treatment for LVO stroke than rt-PA. As with IV rt-PA, time to treatment is a crucial factor for EVT, with high impact on outcomes. Unlike IV rt-PA, EVT is only available at a limited number of stroke centres. This can make the prehospital assessment of patients with stroke a complex process, where efficacy of treatment must be weighed against availability in order to select the most appropriate triage for the patient.[2]

In a review article, Lima and colleagues recommend that regional systems of acute stroke care should be developed to include:

- Rapid identification of suspected stroke
- Centres that provide initial emergency care, including administration of IV rt-PA (e.g. primary stroke centres [PSCs])
- Centres that can perform EVT with comprehensive periprocedural care, to which rapid transport can be arranged when appropriate (e.g. comprehensive stroke centres [CSCs])

The authors highlight the consequences of suboptimal patient triage in such a system. Bypassing the closest PSC in order to transport the patient to a CSC may decrease the chances of the patient receiving IV rt-PA, delay IV rt-PA treatment, and unnecessarily occupy CSC beds if the patient could have been well cared for at a closer PSC. Going to the closest PSC rather than to a CSC may prolong the time to EVT or mean that EVT is not possible at all.

Lima and colleagues note that the development of prehospital assessment scales that are easy and quick to perform and are accurate for detecting LVO strokes is therefore of paramount importance. The development of new technologies to aid in real-time decision making could also simplify the logistics of regional systems of acute stroke care and help select the most appropriate recanalization strategy and destination centre. There should also be organized protocols for interhospital transfer of patients from PSCs to CSCs. The time from PSC arrival to PSC departure should be just as critical a metric of PSC performance as door-to-needle time.

CRITICAL CARE RESUSCITATION UNITS CAN SUPPORT IN THE TREATMENT OF LARGE VESSEL OCCLUSION STROKE

A recent study assessed outcomes after treatment of LVO-AIS in a critical care resuscitation unit (CCRU) compared with a neurocritical care and emergency neurology unit (NCCU) within the same hospital.[3] The CCRU was created to manage patients with a range of critical, time-sensitive conditions, and can accommodate patients with LVO-AIS when the NCCU is full.

Among 128 patients who were transferred to the hospital and underwent MT, 68% were admitted to the CCRU and 32% to the NCCU. The two groups had similar baseline characteristics. The median time from consultation (and request for transfer) to arrival was shorter for CCRU patients than for NCCU patients (86 vs 100 minutes, respectively). The 90-day mortality and proportion of patients with modified Rankin Scale (mRS) score ≤2 were not statistically different between the two groups.

The authors conclude that the CCRU facilitated an increased volume of patients treated with MT for LVO-AIS and reduced the time from consultation to arrival. Outcomes for patients initially treated in the CCRU were similar to those for patients treated in the NCCU, demonstrating that the multi-specialty resuscitation unit complemented the subspecialty unit for care of patients in the hyper-acute phase of an ischaemic emergency.

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Study details

- Retrospective cohort study of data from 128 patients who were transferred from a referring hospital to a tertiary academic centre and underwent endovascular thrombectomy (1 January 2015–31 December 2017)
- The academic centre includes a six-bed CCRU, created in July 2013. Usually, patients with AIS who are transferred to the centre would go to the subspecialty NCCU. However, when a bed is not immediately available in the NCCU, the patient is transferred to the CCRU to minimize delay and allow immediate evaluation and intervention
- The primary outcome was the time interval from transfer request to arrival at the academic centre (Consult–Arrival)
- 87 patients (68%) were initially admitted to the CCRU and 41 (32%) to the NCCU
- Baseline characteristics were similar between the two groups, including the percentage who received IV rt-PA prior to arrival (63% in the CCRU group and 58% in the NCCU group; *p*=0.61)
- Median Consult–Arrival time was lower for CCRU patients than for NCCU patients (see table). The median intervals from arrival at the centre to interventions such as angiography or recanalization were similar between groups
- The proportion of patients who achieved good reperfusion (Thrombolysis In Cerebral Infarction [TICI) scale score 2b or 3) and the proportion with 90-day mRS scale score ≤2 were similar between groups (see table)
- Multivariable logistic regression showed that each minute delay in the interval from transfer request to arrival was associated with a 2.3% increase in the likelihood of death

Variable	CCRU (n=87)	NCCU (n=41)	*p* value
Time interval, median (interquartile range), min			
Consult–Arrival	86 (88–109)	100 (77–127)	0.031
Arrival–Angiography suite	31 (23–47)	30 (21–47)	0.21
Arrival–Skin puncture	49 (37–65)	45 (32–64)	0.24
Arrival–Recanalization	98 (76–122)	118 (80–138)	0.14
Last known well–Arrival	227 (190–301)	245 (218–339)	0.25
Last known well–Recanalization	325 (279–441)	365 (317–443)	0.13
Good reperfusion, TICI scale score 2b or 3, n (%)	80 (92)	36 (88)	0.35
90-day mRS score ≤2, n (%)	36 (41)	17 (41)	0.86
Mortality, n (%)	13 (15)	12 (29)	0.056

"A resuscitation unit can complement the neurocritical care and emergency neurology unit to care for patients in the hyper-acute phase of LVO-AIS"[3]

TENECTEPLASE DISSOLVED CLOTS MORE EFFECTIVELY THAN rt-PA *IN VITRO*

Although rt-PA remains the standard treatment within 4.5 hours of onset of ischaemic stroke, research continues into finding alternative fibrinolytic drugs. TNK is a fibrinolytic treatment used in the acute phase of myocardial infarction. An *in vitro* study has compared the thrombolytic efficacy of TNK and rt-PA, with and without additional ultrasound treatment, as assessed by their effect on the weight and fibrin fibre density of blood clots.[4]

Compared with controls, both rt-PA and TNK significantly increased blood clot weight loss, with and without ultrasound. Both TNK groups (with and without ultrasound) showed significantly increased weight loss compared with their counterpart rt-PA group. Ultrasound did not significantly increase clot dissolution with TNK or rt-PA. Both TNK groups had reduced fibrin fibre density versus the control group, as assessed by transmission electron microscopy. The TNK-alone group also had significantly lower fibrin density than both rt-PA groups.

The authors conclude that in this experimental setting TNK is more effective than rt-PA at dissolving blood clots, both with and without ultrasound. They believe this to be due to TNK having increased specificity to fibrin.

AIS, acute ischaemic stroke; CCRU, critical care resuscitation unit; CI, confidence interval; CSC, comprehensive stroke centre; CT, computed tomography; EVT, endovascular therapy; IV, intravenous; LVO, large vessel occlusion; MR, magnetic resonance; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NCCU, neurocritical care and emergency neurology unit; PSC, primary stroke centre; rt-PA, recombinant tissue plasminogen activator; TICI, Thrombolysis In Cerebral Infarction; TNK, tenecteplase

References

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