From the session "Neurological consequences of intensive care" of the Swiss Neurological Society Congress 2014

Stroke-unit treatment: long-term effects

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Summary

Since the 1990s, stroke units have emerged as core elements in effective acute stroke treatment. Consistent adherence to key processes of stroke care, primarily based on efficient organisational structures, has been the cornerstone of success. On the basis of huge datasets of high quality there is now conclusive evidence of the significant contribution of stroke unit care to diminished mortality and functional dependency in the long term. In the subjective awareness of the affected individuals quality of life has improved considerably. Meanwhile the concept has emerged as a platform for new ideas and research promoting stroke care and early neurorehabilitation. This dynamic process includes exploring specific treatment of comorbidities and the prevention of early recurrence of stroke, as well as the contribution of occupational and speech and language therapy in the acute phase and their interaction with long-term outcome. Current issues include strategies in assessment and treatment of atrial fibrillation, hypertension and diabetes mellitus at hyperacute and acute stage, models of prognostic value in dysphagia used to prevent its inherent risks, and concepts of early language and speech therapy to enhance functional communication. In neurorehabilitation, targeted treatment referred to pathophysiological mechanisms and perception of idiosyncratic in addition to common aspects of functional impairment are major concerns.

Key words: stroke ward; stroke care; selected comorbidities in stroke; stroke recurrence; mortality and dependency; long-term quality of life

Introduction

The effect of stroke-unit treatment has now been evaluated for more than 20 years. Its history has its own logic. Primarily, global effects were the focus of interest: data concerning mortality rates and independence of individuals in daily life after a stroke. More and more finer measures were integrated into the scope such as aspects of mental and physical health and their dependence on initial stroke-unit treatment. The data analyses were designed as a proof of concept in order to justify the related structural efforts and financial investments.

Various questions arise such as: Did we get evidence for more than a global net effect as a result of structures and teams devoted to the needs of acute stroke medicine? Did we acquire specific knowledge improving quality of decisions in a stroke ward and contributing significantly to the well-being and social integration of individuals in the long term?

General aspects: stroke ward versus general ward

A multitude of papers deals with general aspects of stroke units and their interrelation. In the following, an arbitrary selection of a few papers marks essential milestones in establishing the concept of stroke unit in medical practice.

In 1995, the Copenhagen stroke study delivered important and, thus, pivotal data from a comparison of stroke patients from two urban districts with differing treatment concepts, one based in general neurological and medical wards and the other in a dedicated stroke unit [1]. Epidemiological data, including incidence rates of stroke patients admitted to the hospital, were identical in both districts. However, the results of the stroke unit were superior to the traditional general wards in all items tested: early fatal outcome, mortality after 6 months and 1 year, institutional placement and hospital-to-home discharge. In an early monocentric study from Trondheim, Norway, enhanced survival was shown for patients treated in a stroke unit, in comparison with a general ward, as assessed at 6 weeks and up to 5 years after stroke [2]. In detail, the result was not a specific consequence of a particular cause of death, but was a positive net effect obtained in the acute stage that persisted until the end of study. And the proportion of patients at home was higher in those treated in the stroke unit than in the general ward group after 5 years (34.5 vs 18.2%). The positive effects on survival and placement at home were also apparent after 10 years [3]. In a multicentre retrospective study of more than 11,000 patients of Italian hospitals, death and a disabled state were significantly reduced in the long term (with a mean follow-up of about 20 months) provided that hospitalisation in the acute stage was within 48 hours [4].

Subsequent large studies corroborated these findings according to regularly updated Cochrane reviews. The superiority of a stroke ward has now been definitely shown for death and dependence after both short and long intervals, i.e., 3 months and 5 years [5]. A meta-analysis has evaluated the differential effect on ischaemic and haemorrhagic stroke. The direct comparison showed that patients with intracerebral haemorrhage benefit at least as much as patients with ischaemic stroke from patient-organised inpatient care [6]. A recent paper reported stroke-unit care and trends in in-hospital mortality due to stroke in Germany for the period from 2005 to 2010, based on socioeconomic data [7]. The data relied on the nationwide Disease Related Group statistics provided by the Research Data Centre of the Federal Statistical Office; the study included data from more than a million cases, whereof more than 926,000 were treated in the stroke ward of stroke-unit hospitals. The mortality trend shows a significant continuous reduction during the period observed in both stroke wards of stroke-unit hospitals and general wards in non-stroke-unit hospitals, but with a significant difference between types of hospital. The limitations of this study are a result of the administrative hospital dataset: (i.) missing clinical information, such as stroke severity and selection for stroke-unit care in stroke-unit hospitals (accounting on average for a percentage of 65% of acute hospital admissions in 2010), and (ii.) restriction of patient observation to in-hospital stay only. In a recent revision, the general benefit could be characterised by an odds ratio of 0.79 ($p < 0.001$) in favour of stroke-unit admission; this ratio is comparable to the effect size of intravenous thrombolysis with alteplase in comparison to placebo treatment [8]. The stroke-unit concept as the core of modern stroke care may represent a cornerstone that has contributed, among other factors, to the sustained decrease of mortality rate in recent decades [9]. In consequence, the factor stroke unit has been shown to increase definitely the frequency of thrombolysis [10].

Stroke-care characteristics

The aims of stroke care are: (i.) recognition and prevention of general and neurological complications after a stroke by means of continuous monitoring; and (ii.) efficient initiation of diagnostic and therapeutic procedures. In this context a high degree of organisation is a prerequisite, as well as well-established diagnostic and therapeutic algorithms: the standardisation of stroke care should improve collaboration and coordination among partners within a multidisciplinary stroke team. With respect to these processes the Swiss Stroke Society formulated in a consensus paper a profile of requirements for stroke units and stroke centres, defining adequate personnel resources, equipment and infrastructure (Schweizerische Hirnschlaggesellschaft) [11].

It is estimated that 63% of patients will have at least one serious complication following a stroke while staying in a specialised stroke unit [12]. These complications included (with prevalence exceeding 2.5%): pain, elevated temperature, progressing stroke, urinary tract infection, troponin T elevation in the absence of myocardial infarction, chest infection, non-serious falls and myocardial infarction. The process orientation of stroke units offers the opportunity to maximise performance in treating and preventing these complications promptly. Key procedures comprise: timely treatment of infections (most often pneumonia or urinary tract infection); prevention of deep venous thrombosis and pulmonary embolism; screening for swallowing before the patients begin eating, drinking or receiving oral medications; screening for dysphagia and adequate indication for naso-gastral or percutaneous gastrotomy tube; early mobilisation of less severely affected patients; intermittent external compression devices when anticoagulants are contraindicated [10]. A multicentre comparison showed that adherence to key processes of care, such as defined above, was higher in stroke units than in other forms of care [13]. The increased adherence was associated with improved mortality at discharge and, at trend level, greater independence at home. More detailed prevention and treatment of complications, in particular infections, have been shown to contribute significantly to these favourable results [14]. In a recent meta-analysis, discrete stroke units turned out to be more efficient than alternatively organised stroke care, i.e., mobile stroke teams or mixed rehabilitation wards [15].

Acute brain oedema represents a particularly serious complication. In malignant supratentorial stroke, vast surgical decompression is recommended in patients younger than 65 years. Reduced mortality and increased favourable outcomes could be accomplished with early decompression [16]. In large cerebellar infarcts, emergent posterior fossa decompression and removal of infarcted tissue should be done before delayed brain tissue swelling begins independent of age [17, 18].

Selected comorbidities and their management

The study of stroke-unit care and trends in in-hospital mortality due to stroke of Nimptsch and Mansky [7] also provides us with data regarding the proportion of selected comorbidities including atrial fibrillation, hypertension, diabetes, dysphagia and dysphasia/dysarthria, which have been increasingly better documented over the years. This advance suggests an improved perception of the comorbidities implicated in impaired long-term outcomes. Beside global measures, the selected comorbidities outlined above are of major interest, in particular the finding in recent years of new evidence with regard to them. New findings could represent the important basis for evidence-based specific interventions in the stroke unit and refine the concept beyond that implied by global outcome measures.

Atrial fibrillation

In contrast to current guidelines, only a minority (not exceeding 39%) of patients are treated with anticoagulants prior to stroke, a considerable proportion of these at subtherapeutic Ievel [19, 20]. Whereas the use of anticoagulant medication in the acute phase has not yet been investigated, prestroke optimal anticoagulation is associated with better in-hospital outcome and outcome after 2 years in comparison to aspirin medication, suboptimal anticoagulation or no therapy [21].

Furthermore, the detection rate of atrial fibrillation is a crucial parameter in the case of cryptogenic stroke. The rate can be enhanced by pertinacity and prolongation of electrocardiographic monitoring. The specific contribution of a stroke ward has been reported recently by the Heidelberg group. They compared prolonged monitoring over 88 hours (median value) utilising visual assessment as well as a sophisticated automated analysis of a 24-hour Holter electrocardiogram (ECG) [22]. The benefit of prolonged monitoring in the stroke unit was a 2.2% increase in detection of paroxysmal atrial fibrillation by means of visual assessment and a 4.6% increase by means of supplementary automated analysis in comparison with 24-hour Holter ECG. It should be noted that only episodes of at least 30 s were rated as significant, implying that the significance of shorter episodes in the context of acute stroke remains unassessed. In cases of further indication of paroxysmal atrial fibrillation, e.g., a high STAF-Index (Score for Targeting of Atrial Fibrillation) [23], the detection rate can be considerably increased by permanent recording over weeks and months after stroke, as has been shown by the Cristal AF and Embrace studies [19, 24]. It is an open question if paroxysmal atrial fibrillation discovered long after the qualifying event is indicative of embolic pathogenesis related to the previous stroke or rather of an unrelated propensity to atrial fibrillation [25].

The Australian national audit of stroke care was the first study which detailed the influence of hospital care procedures on outcomes of stroke patients with atrial fibrillation [26]. It confirmed that, compared with other aetiologies, atrial fibrillation is independently associated with in-hospital mortality and more impairment due to stroke [27]; and it indicated the positive influence on outcome of hospital processes such as management of a stroke unit, swallow assessment within 24 hours and receiving aspirin medication within 48 hours after ischaemic stroke. However, stroke patients with atrial fibrillation were less likely to receive these important stroke care procedures than patients with other aetiologies.

Hypertension in acute stroke

Current guidelines do not recommend blood pressure reduction in the hyperacute and acute phase of stroke unless blood pressure is extremely high or thrombolysis is being considered. In the latter case a target blood pressure of <185 mm Hg is recommended. Recently, three large randomised clinical trials provided no clear advice for intensive blood pressure reduction in the acute stage of stroke (Scandinavian Candesartan Acute Stroke Trial [SCAST] [28], The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial [INTERACT-2] [29], The Chinese Antihypertensive Trial in Acute Ischaemic Stroke [CATIS] [30]). These studies failed to achieve the primary objective of the trial, represented by the composite endpoint of vascular death, myocardial infarction, or stroke during the first 6 months and functional outcome at 6 months in SCAST [28]; combined death and major disability after 3 months in INTERACT-2 [29], or after 14 days or at hospital discharge in CATIS [30]. In INTERACT-2 a scalar analysis of the modified Rankin Scale (mRS) scores showed a benefit at trend level for intensive blood pressure reduction in the acute phase. Meanwhile, two publications reported new findings in the spring of 2014. Manning et al. [31] communicated the results of their post-hoc analysis of the INTERACT-2 trial, which showed that the variability of blood pressure rather than the extent of its reduction in the hyperacute and acute phases is a predictor of poor prognosis. In the second publication, Fischer et al. [32] found that

throughout the acute phase the rise in blood pressure is steeper, the blood pressure higher and the decrease within the first 24 hours more substantial in intracerebral haemorrhage than in ischaemic stroke. Related to this characteristic blood pressure pattern was a correlation between cerebral small vessel disease and cerebral haemorrhage. It should be emphasised that this study compared premorbid levels with poststroke blood pressure levels for the first time. The studies revealed new aspects of hypertension in acute stroke [33]: (i.) blood pressure is significantly raised compared with usual premorbid levels after intracerebral haemorrhage but not after major ischaemic stroke; (ii.) lowering of high systolic blood pressure, with an emphasis on smooth and sustained target-driven control (140 mm Hg) over several days, improves the chances of recovery after intracerebral haemorrhage. These findings provide a potential explanation of why the balance between risks and benefits of lowering blood pressure acutely after stroke might differ between intracerebral haemorrhage and major ischaemic stroke. But we should also consider the relation between cerebral small vessel disease and cerebral haemorrhage. Further research will clarify whether different approaches to treatment of blood pressure have beneficial effects: (i.) exact timing of treatment, (ii.) route and method of administration (intermittent bolus vs continuous intravenous application), and (iii.) class of drugs [34]. As to the latter one should mention: variation in systolic blood pressure seems to be reduced by calcium channel blockers and non-loop diuretics and increased by angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and beta-blockers [35].

Diabetes mellitus

Diabetes mellitus is a general risk factor related to poor functional outcome after stroke. In predictive risk modeling both with and without intravenous administration of tissue plasminogen activator, initial increased blood glucose is one of several risk factors associated with poorer outcomes [36–38]. The risk of severe intracranial haemorrhage following systemic thrombolysis must be considered. Proposed pathophysiological mechanisms are oxidative stress of ischaemic parenchyma and vasculature, reperfusion injury, and blood–brain barrier disruption [39, 40]. In serial measurements high blood glucose after intravenous thrombolysis, mean blood glucose and maximal blood glucose have been shown to be independently associated with poor outcome at 3 months [41]. Currently a Stroke Hyperglycemia Insulin Network Effort (SHINE, USA) trial is under way and is assessing the efficacy of continuous insulin infusion (target 80–130 mg/dl) compared with the standard subcutaneous insulin-sliding scale (target ≤180 mg/dl) in hyperglycaemic ischaemic stroke patients within 12 hours of symptom onset [42]. Randomisation in the trial will be stratified by intravenous tissue plasminogen activator (tPA) treatment in order to balance the number of thrombolysis patients in the two treatment arms.

Dysphagia

Deglutition disorders after ischaemic stroke occur in up to 40% of patients with a hemispheric lesion and 55% of patients with both hemispheric and brain stem lesions [43]. Dysphagia is associated with lower functional independence measurement and specifically with aphasia and dysarthria [44]. Potential complications are early aspiration and associated chest infection, malnutrition and dehydration [45]. Thus, dysphagia is recognised as an important cause of morbidity and mortality after stroke [46]. To prevent these complications, guidelines recommend: (i.) early nasogastric tube feeding in the presence of aspiration risk and (ii.) percutaneous endoscopic gastrostomy tube feeding if impairment of oral intake is likely to persist for more than 4 weeks [47, 48]. In a multivariate model of extended (greater than 7 days) versus transient (less than 7 days) risk of aspiration, a combined lesion of the frontal operculum and insular cortex was the only significant independent predictor of poor recovery [49]. Discrimination between extended and transient risk of aspiration has been based on a score of 2 out of 6 on the scale of Daniels et al. [50]. However, reliable prognostic criteria to predict impaired deglutition for periods greater than 4 weeks are not available. Individuals restricted to only one food consistency, with or without compensation (assistance and/or texture-modified diets), undergo severe long-term risks: fluid intake (ml/kg/d) is significantly reduced with no diet compared with diet with enteral/parenteral fluid ($p < 0.001$) [51], and both energy and protein consumption ($p < 0.0001$ and $p < 0.003$, respectively) have been shown to be severely diminished [52]. Thus, long-term dysphagia after stroke is a major concern.

Our preliminary data show pronounced dynamics of food restriction in unselected patients after supra- and infratentorial strokes: (i.) a high recovery rate in the first week and (ii.) significantly impaired deglutition persisting throughout 4 weeks in more than 30% (unpublished data). From a practical point of view a prognostic model is needed in stroke care to describe

the recovery characteristics of swallowing based on dysphagia assessment. Accurate prediction of swallowing after dysphagic stroke is important to guide therapeutic decisions and reduce the associated long-term risks.

Dysarthria/dysphasia

In Switzerland the incidence of aphasia due to first stroke is around 43 per 100,000 inhabitants which translates into 3,440 new aphasics per year, for which advancing age and cardioembolism represent significant risk factors [53]. In an unselected and community-based cohort, 38% of patients showed aphasia at admission and 18% still at discharge [54], which corresponds fairly to the estimated proportion of 30% of all cases in Switzerland. Initial aphasia severity was the only clinical indicator of aphasia outcome. In general, the vast majority of stroke-related aphasics have the potential to recover [55]. In comparison with lack of language treatment, language treatment results in improved functional communication [56]. A debate continues over the effectiveness of intensive treatment with respect to study design, definitions of treatment intensity and measurement of short and long-term changes [57]. Enhanced communication therapy offered by a speech and language therapist and similarly intensive social contacts were equally effective within 2 weeks and 4 months after stroke [58]. According to the American Congress of Rehabilitation Medicine, cognitive-linguistic therapies are recommended for language deficits due to left hemisphere stroke [59]. However, the common practice of early intensive input from a speech and language therapist, relying on different strategies, has to be evaluated (Langhorne et al. [60]). The indirect effects of aphasia after stroke should not be underestimated. In the acute stage aphasia might be a risk factor for delirium, a condition associated with increased mortality and morbidity [61]. In the first 6 months, aphasia is also associated with low mood and depression, a condition heaviliy interfering with long-term quality of life [62]. Thus, these aspects need to be considered in further evaluation of treatment concepts.

The issue of stroke recurrence

The recurrence of stroke after an index stroke is highest in the first 6 months, occurring in approximately 9% of cases [63, 64]. After transient ischaemic attacks (TIA), strokes may follow in up to 15% of cases within 3 months, 12.8% occurring in the first week [65]. The risk depends on the underlying aetiology and can be assessed reliably with the so-called ABCD3-I score [66, 67]. The most important determinants are a symptomatic stenosis of the carotid artery, atrial fibrillation and an acute diffusion-weighted imaging lesion as confirmed by magnetic resonance imaging. On the basis of these aspects a tissue-based definition of TIA has been suggested, at least on prognostic grounds [65]. Thus, discrimination of patients at risk is possible at admission to stroke units where they can be observed and adequate treatment effciently initiated. It has been estimated that 80% of secondary strokes might be prevented by this approach [68]. According to the European stroke organisation guidelines, carotid artery endarterectomy (CEA) should be performed as soon as possible after the last ischaemic event, within 2 weeks at the most [69]. In the case of unstable neurological status, efficacy of prompt CEA is not well established [10]. However, the question of the optimal timing of intervention in the individual case of symptomatic carotid artery remains to be answered [70].

Structure of stroke care interfering with the long-term quality of life

An early report from Indredavik et al. deals with quality of life after treatment in a stroke unit [71]. Based on the Nottingham Health Profile, stroke-unit treatment showed a better and more sustained effect on different aspects of well-being. Patients who survived their stroke for 5 years did better in many aspects such as energy, emotional reactions, social isolation, physical mobility and sleep. Patel et al. [72] described clinical determinants of long-term quality of life 1 year after stroke. Poor physical health 1 year after stroke has been associated independently with being female, or a manual worker, or having diabetes mellitus, right hemispheric lesions, urinary incontinence, or cognitive impairment. Partly differing from these findings, poor mental health 1 year after stroke has been associated independently with being under 65 years old, or being Asian, or having ischaemic heart disease or cognitive impairment.

The impact of integrated care pathways (ICP) in organised stroke rehabilitation has been explored by Sulch et al. [73]. ICP envisaged therapeutic interventions grouped according to stage and patient needs predicted in advance. Contrary to expectations, a conventional consultant-led multidisciplinary team was superior to ICP with respect to quality of life after 6 months as assessed with the EuroQoL visual analogue scale and the subitem “social functioning”. The study points out the important fact that idiosyn-

cratic aspects of stroke patients are at risk of being overlooked by a rigid ICP approach focussed on the common needs of all stroke patients. In a Spanish study, functional status and depression were identified as predictors for quality of life 1 year after stroke [74]. An interesting concept of a stroke unit combined with supported early discharge has been reported by Fjaertoft et al. [75]. Such an extended stroke-unit service improved long-term clinical outcome after 1 year compared with care on an ordinary stroke-unit care: a significantly higher proportion of patients were independent and patients with moderate to severe stroke profited most.

Future research has to address the complex factors that determine health-related long-term quality of life. These include (i.) critical physical disability and targeted neurorehabilitative treatment [76], and (ii.) cognitive impairment, in particular the consequences of right hemispheric lesion such as neglect, anosognosia and spatial disorientation [72, 77]. These factors impact the optimal organisational structures of stroke care. From the viewpoint of socioeconomic interest, the efficiency of two stroke unit concepts has been compared recently, colocated acute/rehabilitation stroke care vs traditionally separated acute/rehabilitation stroke care. The colocated concept has proved to be slightly more efficient as a function of time according to functional independence measurement [78].

Conclusions

1. There is now definite evidence that the stroke unit concept has significant beneficial effects in the long term with decreased mortality and diminished dependency after stroke. In these respects patients suffering both ischaemic and haemorrhagic stroke profit to the same degree.
2. There is also evidence for sustained better quality of life after stroke in the long term. Consideration of specific aspects of physical and mental health may provide enhanced understanding of the nature of quality of life.
3. The type of discrete, spatially defined stroke unit has been shown to represent the most appropriate and efficient organisational structure. Well-established diagnostic and therapeutic algorithms ensure adherence to the basic key procedures of stroke care which are essential to a good outcome.
4. Stroke units play a central role in neurovascular research, development of procedures and dissemination of new strategies in stroke care and rehabilitation. These include the treatment of comorbidities, the quality of neurorehabilitation services and occupational therapy as well as the clear communication of rehabilitation aims in the transition from inpatient treatment to outpatient care.

Disclosures

No financial support and no other potential conflict of interest relevant to this article was reported.

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