ORIGINAL CONTRIBUTIONS

Does the Prevention of Complications Explain the Survival Benefit of Organized Inpatient (Stroke Unit) Care?

Further Analysis of a Systematic Review

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ABSTRACT: ***Background and Purpose***— Systematic reviews have shown that organized inpatient (stroke unit) care reduces the risk of death after stroke. However, it is unclear how this is achieved. We tested whether stroke unit care could reduce deaths by preventing complications.***Methods***— We updated a collaborative systematic review of 31 controlled clinical trials (6936 participants) to include reported interventions and complications during early hospital care plus the certified cause of death during follow up. Each secondary analysis used data from between 7 and 17 studies (1652 to 3327 participants). Complications were grouped as physiological, neurological, cardiovascular, complications of immobility, and others. Bayesian hierarchical models were used to estimate odds ratios for features occurring in stroke units versus conventional care.***Results***— Based on the data of 17 trials (3327 participants), organized (stroke unit) care reduced case fatality during scheduled follow up (OR: 0.75; 95% credible intervals: 0.59 to 0.92), in particular deaths certified as attributable to complications of immobility (0.59; 0.41 to 0.86). Stroke unit care was associated with statistically significant increases in the reported use of oxygen (2.39; 1.39 to 4.66), measures to prevent aspiration (2.42; 1.36 to 4.36), and paracetamol (2.80; 1.14 to 4.83) plus a nonsignificant reduction in the use of urinary catheterization. Stroke units were associated with statistically significant reductions in stroke progression/recurrence (0.66; 0.46 to 0.95) and in some complications of immobility: chest infections (0.60; 0.42 to 0.87), other infections (0.56; 0.40 to 0.84), and pressure sores (0.44; 0.22 to 0.85). There were no significant differences in cardiovascular, physiological, or other complications.***Conclusions***— Organized inpatient (stroke unit) care appears to reduce the risk of death after stroke through the prevention and treatment of complications, in particular infections.

Key Words: complications ■ meta-analysis ■ stroke outcome ■ stroke units

It has been known for many years that organized inpatient (stroke unit) care reduces the risk of death after stroke,[1] but it is not clear how this benefit is achieved. The Stroke Unit Trialists Collaboration carried out an analysis 10 years ago that suggested that stroke units may reduce deaths through preventing complications.[2] However, this analysis had limited statistical power and its conclusions were speculative.

In the most recent update of the stroke unit systematic review,[3] data were available from a larger number of controlled clinical trials. This allowed us to revisit the question "does the prevention of complications explain the survival benefit of stroke unit care?" If this is the case, then we would expect the following observations to be associated with stroke unit care: (1) the more frequent use of interventions designed to prevent complications; (2) a smaller number of recorded serious complications; and (3) fewer deaths attributed to complications.

We report a further analysis of the stroke unit review that addresses these questions.

METHODS

Methods of the Review

This is a further analysis of a collaborative systematic review carried out by the Stroke Unit Trialists Collaboration.[3] In summary, this involved rigorous searching for clinical trials of organized inpatient (stroke unit) care, the formation of a collaborative group comprising the primary trialists, the collation of extensive descriptive information and outcome data, and the analysis of these data using rigorous meta-analysis methods. For the current analysis, we used a very broad definition of stroke unit care and included any trial that compared organized (stroke unit) care (defined as a multidisciplinary team specializing in stroke care) versus the contemporary conventional care such as a general medical ward or less organized form of stroke care. Stroke unit care could include services based in a discrete ward or provided by a mobile stroke team. In addition to the existing data, we sought information on the following outcomes: (1) specific interventions directed at reducing complications; (2) complications recorded during early hospital care (first 4 weeks); and (3) certified cause of death during follow up. The exact criteria used were those defined in the individual trials.

The majority of trials recorded cause of death at the end of scheduled follow up with the exception of three trials that recorded at discharge,[4–6] three trials that recorded at an earlier fixed time point,[7–9] and one trial with incomplete data.[10] The median time for recorded cause of death was 6 months with an interquartile range of 3 to 12 months.

Complications were classified into four categories to reflect previous epidemiological work linking complications to cause of death[11]: (1) neurological (cerebral edema, stroke recurrence, stroke progression, seizures, anxiety, depression); (2) cardiovascular complications (myocardial infarction, arrhythmia, congestive cardiac failure); (3) complications of immobility (chest infection, urinary tract infection, other infections, dehydration, venous thromboembolism, falls, pressure sores, pain); and (4) other complications (eg, cancer, gastrointestinal hemorrhage, suicide).

In addition, we also recorded common "physiological complications," which were defined as physiological abnormalities that did not fulfill a conventional medical diagnosis. These included hypertension, hyperglycemia, hypoxia, hypotension, and pyrexia. The specific definitions of these complications were reported within the original trials.

The specific interventions directed at reducing complications included antibiotics, measures to prevent aspiration (systematic assessment of swallowing and modification of dietary intake), fluids, insulin, oxygen, paracetamol, tube feeding, and urinary catheterization.

Statistical Methods

Data were analyzed using a hierarchical Bayesian approach[12] in WinBUGS. A direct random effects model was used to calculate ORs and 95% credible intervals (CrI). The direct model does

not require the assumption of normality for the raw data because it allows us to directly model the numbers of patients with particular outcomes. The assumption of normality can often fail when there are small numbers of trials or events within trials therefore this is a great advantage in this analysis. The random effects model allows the calculated study-specific effects (log ORs) to be different from each other but assumes they are from a common distribution, in this case the Normal distribution. In other words, it assumes that all trials are similar but not identical.[13] The fitted model was checked for adequacy and found to be acceptable. Sensitivity for the range of assumptions required for this model was also checked.
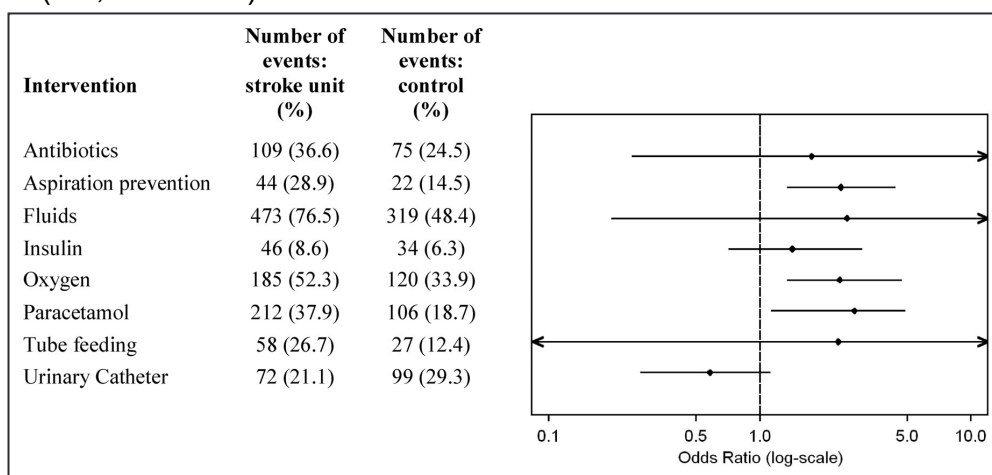
In addition, absolute risk differences were calculated using the DerSimonian and Laird[14] approach using Revman software.[15] This is a variation on the inverse-variance method that weights trials according to the extent of variation among treatment effects across trials.[14] The DerSimonian and Laird approach also adjusts the standard errors of the trial-specific effects to incorporate a measure of the extent of heterogeneity among treatment effects observed in different trials.[14]

RESULTS

The updated systematic review contains 31 controlled clinical trials (6936 participants).[3] A subset of these trials was able to provide much more detailed data for further analyses as outlined subsequently. Further details of the included trials are summarized in a related review.[3]

Interventions to Prevent Complications

Data were available for seven trials (1652 participants).[8,16–21] The results of this analysis are shown in Figure 1, which indicated that the use of the following interventions were significantly associated with stroke unit care: measures to prevent aspiration (OR: 2.4; 95% CrI: 1.4 to 4.4); oxygen therapy (2.4; 1.4 to 4.7); paracetamol (2.8; 1.1 to 4.8); and possibly a reduced use of urinary catheter (0.6; 0.3 to 1.1).

Intervention	Number of events: stroke unit (%)	Number of events: control (%)	
Antibiotics	109 (36.6)	75 (24.5)	
Aspiration prevention	44 (28.9)	22 (14.5)	
Fluids	473 (76.5)	319 (48.4)	
Insulin	46 (8.6)	34 (6.3)	
Oxygen	185 (52.3)	120 (33.9)	
Paracetamol	212 (37.9)	106 (18.7)	
Tube feeding	58 (26.7)	27 (12.4)	
Urinary Catheter	72 (21.1)	99 (29.3)	

Figure 1. Frequency of intervention use in stroke units and conventional care. Results in plot are presented as (median) ORs of use of interventions in stroke units versus conventional care. ORs are represented by the shaded diamond with corresponding 95% CrIs represented by the line. Results are plotted on the log scale.

Complications During Acute Hospital Stay

Complications data were available for eight trials (1824 participants).[6,8,18–23] The main findings are summarized in Table 1. Statistically significant reductions in complications were seen in stroke

units for the examples of stroke progression or recurrence, chest infection, other infections, falls, and pressure sores. None of the recorded physiological complications were significantly reduced (Figure 2).

TABLE 1. Comparison of Complications Occurring in Stroke Units Versus Conventional Care (Table view)

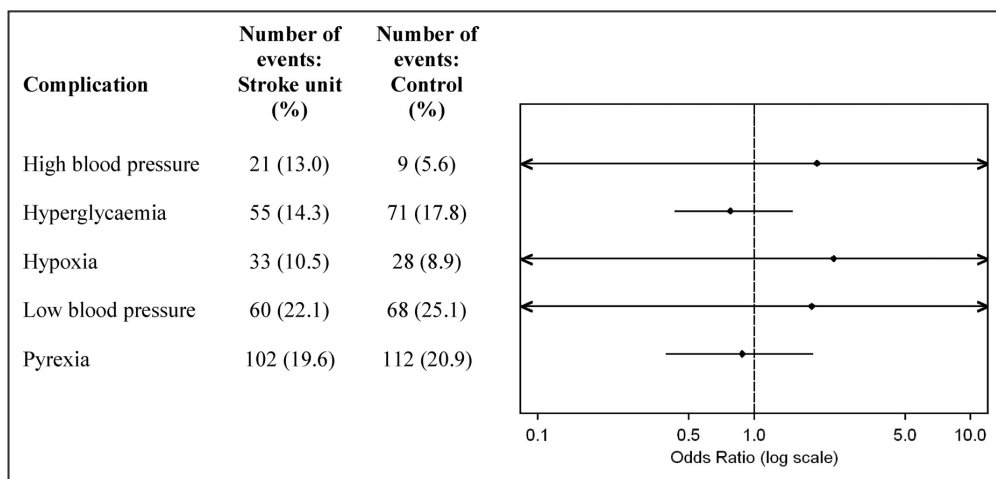| Outcome/Category	No. of Events: Stroke Unit (%)	No. of Events: Control (%)	OR (median)	95% CrI
Neurological				
Anxiety or depression	112 (16.7)	132 (19.7)	0.74	(0.27–1.97)
Seizures	15 (2.7)	17 (3.1)	0.86	(0.37–1.95)
Stroke progression or recurrence*	85 (9.4)	121 (13.5)	0.66	(0.46–0.95)
Cardiovascular				
Cardiovascular†	83 (14.2)	66 (11.0)	1.52	(0.58–4.54)
Complications of immobility				
Chest infection	87 (12.0)	134 (18.6)	0.60	(0.42–0.87)
Other infections‡	122 (13.5)	201 (21.9)	0.56	(0.40–0.84)
Dehydration	21 (5.1)	43 (10.1)	0.81	(0.31–2.53)
Venous thromboembolism§	30 (4.4)	35 (5.0)	0.85	(0.49–1.49)
Falls	28 (18.4)	43 (28.3)	0.57	(0.33–0.97)
Pressure sores	21 (4.7)	43 (9.6)	0.44	(0.22–0.85)
Pain	70 (12.1)	71 (12.3)	0.73	(0.14–2.60)
Other complications				
Other	22 (2.9)	24 (3.1)	0.95	(0.46–2.10)
Results are presented as ORs with 95% CrI of complications in stroke units versus conventional care.				
*Stroke progression and early recurrence were often not distinguished in the original trials.				
†Individual cardiovascular complications (eg, ischemic heart disease, arrhythmia) were usually grouped together.				
‡Predominantly urinary tract infection.				
§Includes deep vein thrombosis and pulmonary embolism.				

Complication	Number of events: Stroke unit (%)	Number of events: Control (%)	
High blood pressure	21 (13.0)	9 (5.6)	
Hyperglycaemia	55 (14.3)	71 (17.8)	
Hypoxia	33 (10.5)	28 (8.9)	
Low blood pressure	60 (22.1)	68 (25.1)	
Pyrexia	102 (19.6)	112 (20.9)	

Figure 2. Frequency of physiological complications in stroke units or conventional care. Results are presented as in Figure 1.

Certified Cause of Death

Information on certified cause of death was available for 17 trials (3327 participants).[4–10,18,19,21,23–29] Within this group of trials, organized (stroke unit) care resulted in reduced all-cause case fatality (OR: 0.75; 95% CrI: 0.59 to 0.92). The results for certified cause of death are summarized in Table 2 and indicated that significant reductions in deaths were observed for complications of immobility (0.59; 0.41 to 0.86) but not for any other categories. When these are analyzed as absolute risk difference, we see that there is a reduction in deaths attributed to complications of immobility of approximately one to 2 deaths per 100 patients with stroke.

TABLE 2. Comparison of Certified Cause of Death in Stroke Unit Versus Conventional Care (Table view)

Cause of Death	Stroke Unit (%)	Control (%)	Absolute Risk Difference	95% CI	P^*	OR (median)	95% CrI
Neurological	8.1	7.8	0	(−1, 1)	0.92	1.07	(0.81–1.44)
Cardiovascular	3.6	4.9	−1	(−2, 1)	0.47	0.71	(0.45–1.10)
Immobility-related	4.4	7.0	−1	(−3, 0)	0.06	0.59	(0.41–0.86)
Other	2.4	3.2	0	(−1, 0)	0.39	0.74	(0.47–1.17)
Overall	18.5	23.0	−3	(−6, 0)	0.04	0.75	(0.59–0.92)
Percentages (%) are the percentage of total patients in each group that died from a particular cause of death. Absolute risk difference is given as number of deaths per 100 patients with stroke with corresponding CI and P value. ORs are given as in Table 1.							
*P value is associated with the absolute risk difference result.							

We carried out sensitivity analysis because Bayesian analyses can be sensitive to the choice of priors and initial values. The conclusions were unaffected by choice of prior distribution and initial values.

DISCUSSION

It has been recognized over the last decade that patients who are managed in an organized inpatient (stroke unit) setting are more likely to survive, return home, and regain independence

than those managed in conventional care settings.[1] However, there has been considerable uncertainty as to why this benefit may occur and how stroke unit care could influence outcomes. In a previous analysis from the Stroke Unit Trialists Collaboration,[2] it was suggested that some of the survival benefit of stroke unit care may be explained by a reduction in complications. However, there was limited statistical power to carry out this analysis. In the current update, we had access to considerably larger amounts of data, which indicated that stroke unit care appeared to reduce complications of immobility (in particular, infections), although there were also reductions in stroke recurrence or progression. The current analysis suggests that some of these reductions could be explained by a more comprehensive implementation of measures to prevent complications, in particular, measures to prevent aspiration, oxygen treatment, and treatment for pyrexia.

Although our analysis has a number of strengths, in particular using a much larger data set than previously available, we must also acknowledge a number of limitations. First, although we have carried out a pooled analysis of a number of trials, there is still limited information around particular complications and CIs are correspondingly broad. Second, we have used trial data in which some complications were often not recorded in a blinded fashion and variable definitions of complications may have been used. For example, it was often difficult to distinguish between the complications of very early stroke recurrence and progression of the original stroke symptoms. Therefore, the current analysis may have been subject to observer bias. Similarly, the information on certified cause of death is frequently not confirmed by postmortem examination and so could also be subject to bias. Third, the analysis of complications may be difficult to interpret. In theory, careful monitoring could identify and treat more problems than those identified in a less careful model of care. Fourth, early mobilization and training was reported as an objective of care in most of the included trials; however, no standard definition of measuring mobilization was used. Therefore this potentially important aspect of care could not be analyzed. Likewise, other components of stroke unit care (eg, prompt use of antithrombotic drugs, improved monitoring) could not individually be analyzed. Finally, our analysis demonstrates an association between stroke unit care and reduction in certain complications but does not explain how this effect was achieved.

Although we propose that stroke unit care may have helped prevent complications, the picture is likely to be complex and there are other possibilities. It is plausible that early stroke unit care could have resulted in patients having less disabling symptoms and hence were less prone to experience complications. Physiological consequences of other complications (for example, pyrexia attributable to aspiration pneumonia) may cause secondary dysfunction or cell death in the penumbral area. In the acute phase of ischemic stroke, this can lead to stroke progression and worsening of the prognosis. Complications in the chronic phase probably influence mortality directly. It is also plausible that if patients in stroke units are less likely to die through other (identified) mechanisms, they would also be less likely to experience complications associated with the last stages of life. Our analysis cannot conclusively discriminate between these competing possibilities.

Despite these remaining uncertainties, we conclude that our findings emphasize the potential importance of complications as a treatable factor in stroke outcome. Future research should explore the best ways of preventing and managing specific complications, particularly those that seem to carry a high risk of causing harm.

ARTICLE INFORMATION

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Acknowledgments

REFERENCES

1. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *BMJ.* 1997; *314*: 1151–1159. Crossref. PubMed.

2. Stroke Unit Trialists' Collaboration. How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. *Stroke.* 1997; *28*: 2139–2144. Crossref. PubMed.

3. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev.* 2006; *2*: CD000197.

4. Gordon EE, Kohn KH. Evaluation of rehabilitation methods in hemiplegic patient. *J Chronic Dis.* 1966; *19*: 3–16. Crossref. PubMed.

5. Yagura H, Miyai I, Suzuki T, Yanagihara T. Patients with severe stroke benefit most by interdisciplinary rehabilitation team approach. *Cerebrovasc Dis.* 2005; *20*: 258–263. Crossref. PubMed.

6. Cavallini A, Micieli G, Marcheselli S, Quaglini S. Role of monitoring in management of acute ischemic stroke patients. *Stroke.* 2003; *34*: 2599–2603. Crossref. PubMed.

7. Vemmos K, Takis K, Madelos D, Synetos A, Volotasiou V, Tzavellas H. Stroke unit treatment versus general medical wards: long term survival. *Cerebrovasc Dis.* 2001; *11*: 8.

8. Kalra L, Evans A, Perez I, Knapp M, Donaldson N, Swift CG. Alternative strategies for stroke care: a prospective randomised controlled trial. *Lancet.* 2000; *356*: 894–899. Crossref. PubMed.

9. Hamrin E. Early activation in stroke—does it make a difference? *Scand J Rehabil Med.* 1982; *14*: 101–109. PubMed.

10. Aitken PD, Rodgers H, French JM, Bates D, James OFW. General medical or geriatric unit care for acute stroke? A controlled clinical trial. *Age Ageing.* 1993; *22*: 4–5. Crossref.

11. Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of a 1st stroke—the Oxfordshire-Community-Stroke-Project. *J Neurol Neurosurg Psychiatry.* 1990; *53*: 824–829. Crossref. PubMed.

12. Spiegelhalter DJ, Thomas A, Best NG, Lunn D. *WinBUGS version 1.4 user manual.* Cambridge: MRC Biostatistics Unit; 2003. Available at: www.mrc-bsu.cam.ac.uk/bugs. Accessed 2006.

13. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Stat Med.* 1995; *14*: 2685–2699. Crossref. PubMed.

14. Deeks JJ, Higgins JPT, Altman DG. Analysing and presenting results. In: Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5[updated May 2005]; Section 8. In: The Cochrane Library, Issue 3. Chichester: John Wiley & Sons, Ltd; 2005.

15. The Cochrane Collaboration. *Review Manager (RevMan). Version 4.2 for Windows.* Copenhagen: The Nordic Cochrane Centre; 2003. Available at: www.cc-ims.net/RevMan. Accessed 2006.

16. Ronning OM, Guldvog B. Stroke unit versus general medical wards, II: Neurological deficits and activities of daily living—a quasi-randomized controlled trial. *Stroke.* 1998; *29*: 586–590. Crossref. PubMed.

17. Patel N. Organised care of acute stroke at Goort Schuur Hospital. MPhil in Epidemiology. University of Cape Town, Cape Town, South Africa; 2000. Thesis.

18. Sulter G, Elting JW, Langedijk M, Maurits NM, De Keyser J. Admitting acute ischemic stroke patients to a stroke care monitoring unit versus a conventional stroke unit: a randomized pilot study. *Stroke.* 2003; *34*: 101–104. Crossref. PubMed.

19. WoodDauphinee S, Shapiro S, Bass E, Fletcher C, Georges P, Hensby V, Mendelsohn B. A randomized trial of team care following stroke. *Stroke.* 1984; *15*: 864–872. Crossref. PubMed.

20. Kalra L, Dale P, Crome P. Improving stroke rehabilitation: a controlled study. *Stroke.* 1993; *24*: 1462–1467. Crossref. PubMed.

21. Indredavik B, Bakke F, Solberg R, Rokseth R, Haaheim LL, Holme I. Benefit of a stroke unit: a randomized controlled trial. *Stroke.* 1991; *22*: 1026–1031. Crossref. PubMed.

22. Ma RH, Wang YJ, Qu H, Yang ZH. Assessment of the early effectiveness of a stroke unit in comparison to the general ward. *Chin Med J (Engl).* 2004; *117*: 852–855. PubMed.

23. Ilmavirta M. Stroke unit and outcome of brain infarction. Doctor of Medicine Thesis. University of Tampere, Tampere, Finland; 1994(Series A, volume 410).

24. Stevens RS, Ambler NR, Warren MD. A randomized controlled trial of a stroke rehabilitation ward. *Age Ageing.* 1984; *13*: 65–75. Crossref. PubMed.

25. Garraway WM, Akhtar AJ, Hockey L, Prescott RJ. Management of acute stroke in the elderly: follow up of a controlled trial. *BMJ.* 1980; *281*: 827–829. Crossref. PubMed.

26. Sivenius J, Pyorala K, Heinonen OP, Salonen JT, Riekkinen P. The significance of intensity of rehabilitation of stroke: a controlled trial. *Stroke.* 1985; *16*: 928–931. Crossref. PubMed.

27. Dey P, Woodman M, Gibbs A, Steele R, Stocks SJ, Wagstaff S, Khanna V, Chaudhuri MD. Early assessment by a mobile stroke team: a randomised controlled trial. *Age Ageing.* 2005; *34*: 331–338. Crossref. PubMed.

28. Feldman DJ, Lloyd K, Rusk HA, Lee PR, Untereck J, Toole A. A comparison of functionally orientated medical care and formal rehabilitation in management of patients with hemiplegia due to cerebrovascular disease. *J Chronic Dis.* 1962; *15*: 297–310. Crossref. PubMed.

29. Hankey GJ, Deleo D, StewartWynne EG. Stroke units: an Australian perspective. *Aust N Z J Med.* 1997; *27*: 437–438. Crossref. PubMed.