Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Schucht P, Fischer U, Fung C, et al. Follow-up computed tomography after evacuation of chronic subdural hematoma. N Engl J Med 2019;380:1186-7. DOI: 10.1056/NEJMc1812507

Supplementary Appendix

Table of contents

Table 1. Baseline characteristics.

	Overall (n=361)	**CT-arm (n=181)**	**no-CT-arm (n=180)**
Age (mean) in years	73.5	73.7	73.3
Female sex (%)	117 (32)	64 (35)	53 (29)
Symptoms prior to surgery			
GCS<15 (%)	84 (23)	43 (24)	41 (23)
GCS≤8 (%)	2 (0.6)	1 (0.6)	1 (0.6)
Neurological deficits (%)	237 (66)	121 (67)	116 (64)
NIHSS, median	2	2	2
History of falls (%)	76 (21)	33 (18)	40 (22)
Oral anticoagulation (%)	96 (27)	46 (25)	50 (28)
Antiplatelet medication (%)	107 (30)	58 (32)	49 (27)

Hematoma width, mean, in cm	2.05	2.01	2.09
Midline shift mean, in cm	0.74	0.74	0.73
Patients with bilateral CSH (%)	85 (24)	39 (22)	46 (26)

GCS denotes Glasgow coma scale; NIHSS, National Institutes of Health Stroke Scale; MMS, Mini Mental Status.

Table 2. Secondary outcome data.

Re-operations			
	CT-arm	**No-CT-arm**	**Total**
Total number of re-operations	59	39	98
No. of patients who had one or more re-operations	49	34	83
Non-fatal complications			
	CT-arm	**No-CT-arm**	**Total**
Epileptic seizures	5	5	10
Infections at the site of surgery	4	3	7
Deep venous thrombosis	0	2	2
Cerebrovascular infarction	2	0	2
Pulmonary emboli	2	0	2
Myocardial infarction	1	0	1
Total number of non-fatal complications	14	10	24
Mortality			

	CT-arm	No-CT-arm	Total
Cardiac arrest	3	3	6
Ischemic stroke	1	1	2
Pneumonia	1	2	3
Cancer	2	0	2
Multiple organ failure	2	0	2
Suicide	1	0	1
Trauma	1	0	1
Not specified	1	2	3
Total number of deaths	12 (6.7%)	8 (4.7%)	20 (5.4%)
Predefined adverse events			
No. of predefined adverse events	88	59	
Length of hospital stay in days			
	CT-arm	**No-CT-arm**	
Median number	6	6	–

Mean number	9	10	–

Costs in Swiss francs

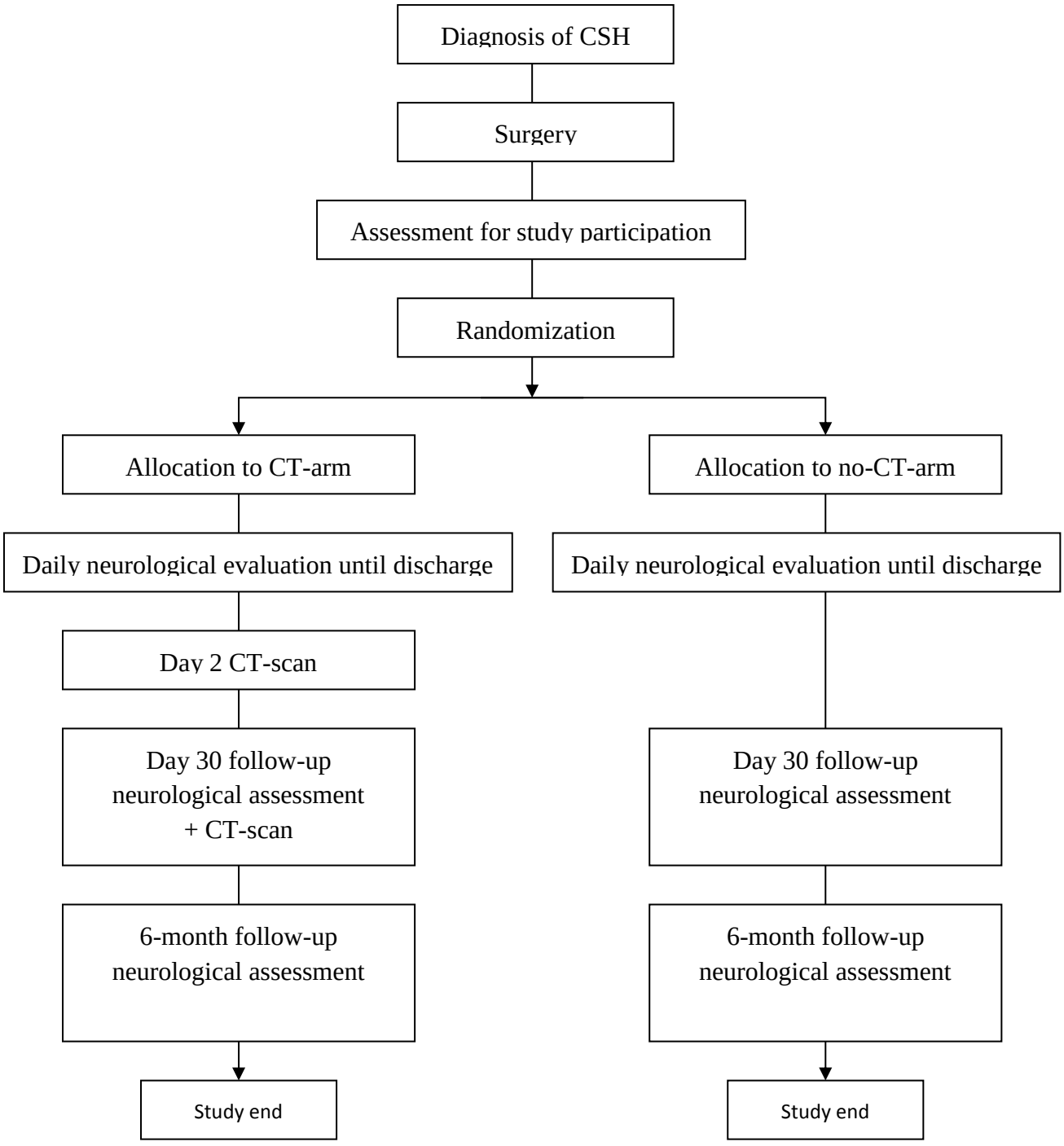
	CT-arm	**No-CT-arm**	**Difference**
Median costs	16,038	14,102	1926
Mean costs	21,298	18,047	3251

Table 3. Clinical and radiological characteristics before re-operation.

	Overall (n=81)	**CT-arm (n=48)**	**no-CT-arm (n=33)**
Symptoms prior to surgery			
GCS<15 (%)	17 (21%)	9 (18.8%)	8 (24.2%)
GCS≤8 (%)	0	0	0
Neurological deficits (%)	42 (51.9%)	19 (39.6%)	23 (69.7%)
NIHSS, median	1	0	1
Hematoma width, mean, in cm	1.93 SD 0.54	1.95 SD 0.47	1.91 SD 0.63
Midline shift mean, in cm		0.59 SD 0.38	0.46 SD 0.35

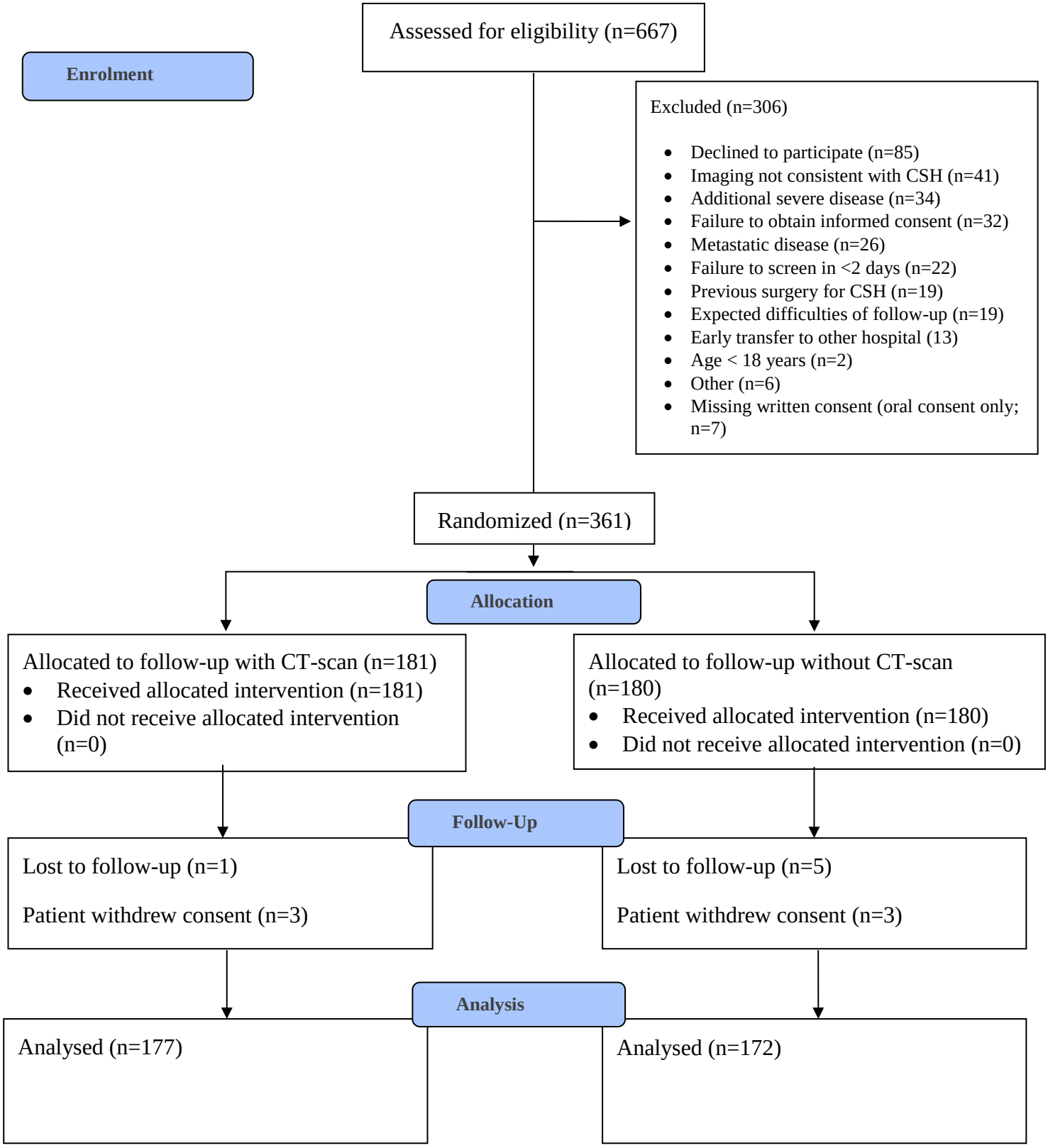
GCS denotes Glasgow coma scale; NIHSS, National Institutes of Health Stroke Scale.

Figure 1. Participant flow.



Note: All patients, independent of allocation to trial arm, received a CT-scan when indicated by persisting or new neurological deficits. CSH denotes chronic subdural hematoma, and CT computed tomography.

Figure 2. CONSORT 2010 flow diagram.



Ethical considerations and trial registration

The study was approved by the local ethics committee (KEK Bern 218/10) and registered (NCT01624545). The article adheres to the CONSORT statement. The trial was registered on clinicaltrials.gov on 20/06/2012 following a delay after the study start on 5/6/2012 due to a misunderstanding in the communication with our clinical trial unit.

We included 4 patients between 05/06/2012 and 20/6/2012 (i.e., between study start and trial registration). Of these, 2 were randomized into the CT arm and 2 into the no-CT arm.

To scan or not to scan? A randomized trial on follow-up of chronic subdural hematoma

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Keywords: chronic subdural hematoma – CSH – follow-up – burr holes

Abbreviations:

CSH: chronic subdural hematoma – CT: computed tomography – NIHSS: National Institutes of Health Stroke Scale – mRS: modified Rankin Scale – MMS: Mini Mental Status

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ABSTRACT

BACKGROUND

Recurrent or persisting chronic subdural hematoma after surgery is frequent. Postoperative computed tomography (CT) often shows substantial residuals and may trigger re-operations. However, the benefit of post-surgical imaging remains unknown.

METHODS

We randomly assigned 361 patients with chronic subdural hematoma within 48 hours after surgery to receive clinical and radiological follow-up with CT imaging 2 and 30 days after surgery (CT-arm; n = 181) or clinical follow-up and CT only in case of neurological deterioration (no-CT-arm, n = 180). The primary endpoint was defined as survival after 6 months without severe disability (modified Rankin scale [mRS] 0–3).

RESULTS

The primary endpoint was available for 349 patients: 160 of 172 (93%) in the no-CT-arm and 157 of 177 patients (89%) in the CT-arm survived with mRS 0–3 (odds ratio 1.74, 95% confidence interval 0.818–3.72, P=0.15). Twelve patients from the CT-arm and 8 patients from the no-CT-arm died. We performed 59 re-operations for recurrent or persisting hematomas on patients in the CT-arm, and 39 in the no-CT-arm. Complications occurred in 26 patients in the CT-arm and in 19 in the no-CT-arm. Follow-up with CT imaging did not improve the primary outcome; the between-arm difference for mRS was not significant.

CONCLUSION

Follow-up with routinely scheduled CT-scans after neurosurgical evacuation of chronic subdural hematoma is not superior to clinical neurological examination alone and CT-scans only in case of clinical deterioration or persisting neurological deficits. (Trial Registration Number: NCT01624545)

Introduction

Most patients recover completely after surgical evacuation of chronic subdural hematoma (CSH), but recurrence rates and re-operations range from 3% to 39%.[1-5] Post-surgical computed tomography (CT) – performed as a baseline test – shows residual blood components in most patients. However, improvement of symptoms does not require their complete removal.

Follow-up CT is used to monitor hematoma residuals; however, there is disagreement about its usefulness to predict symptomatic recurrence.[6] Some centers routinely perform CT imaging after surgery and during follow-up, while others use CT only in cases of clinical deterioration.[7-11]

Routine postoperative CT can potentially detect recurrent CSH before clinical deterioration occurs, but unnecessary revision surgery and increased costs may outweigh this benefit. In this trial we aimed to find out whether routinely scheduled CT has any impact on outcome of CSH.

MATERIALS AND METHODS

Design

This investigator-initiated study was a prospective, 1:1 randomized, controlled trial. Patients were randomly assigned to clinical follow-up combined with CT imaging 2 and 30 days after surgical evacuation of a CSH (CT-arm), or to clinical follow-up and CT only in case of clinical deterioration (no-CT-arm). The diagnosis of CSH was established if (i) pre-operative imaging (CT or magnetic resonance imaging [MRI]) showed a subdural hematoma with or without fresh blood components, and (ii) a non-acute subdural hematoma was confirmed during surgery.

The study was approved by the local ethics committee (KEK Bern 218/10) and registered (NCT01624545). The article adheres to the CONSORT statement. The trial was registered on clinicaltrials.gov following a short delay (14 days) due to a misunderstanding in the communication with our clinical trial unit.

Endpoints

The primary endpoint was defined as favorable outcome at 6 months, assessed with the modified Rankin Scale (mRS). mRS scores of 0–3 were considered favorable. Secondary endpoints included the number of re-operations, complications, mortality, patients with one or more adverse events (death, complications, recurrent or persisting hematomas), days spent in hospital, and costs.

Participants

Inclusion criteria were: (i) newly diagnosed CSH by CT or MRI, operated on within the preceding 48 hours; (ii) age 18 years or older; and (iii) written informed consent from the patient or family. Exclusion criteria were: (i) moribund condition prohibiting surgery; (ii) foreseeable difficulties in

follow-up for geographic reasons; (iii) previous CSH; (iv) spontaneous cerebrospinal fluid (CSF) leak;[12] (v) pregnancy; and (vi) carcinomatous meningitis or metastatic disease with limited life expectancy.

Surgery required placement of 2 burr holes and placement of a drain for 24–48 hours if feasible. Drainage was restricted to 150 ml or less per 24 hours. Low-dose subcutaneous low-molecular-weight heparin was given 36 hours after surgery or after removal of the drain until hospital discharge. The head of the bed was elevated at 15° to 30° and patients were free to ambulate. Antibiotics (cefuroxime, 1.5 g intravenously every 8 hours) were administered until 24 hours after removal of the drain.

Patient allocation

Patient management is shown in Fig. 1. After surgery, patients were randomly allocated to the CT-arm or the no-CT-arm using permuted blocks of length 4 (Random Allocation Software®, V.1.0). Randomization was stratified by pre-surgery intake of any anticoagulants (vitamin K or non-vitamin K antagonists) or antiplatelet medication.

Post-interventional assessments

CT was scheduled on days 2 and 30 after neurosurgical evacuation of the CSH for patients in the CT-arm, but not in the no-CT-arm. Apart from the prescheduled CT-scans on days 2 and 30, the postoperative management of the two trial arms was identical and followed institutional guidelines. After surgical evacuation of the hematoma, patients were transferred to an intermediate care unit for neurological surveillance for 24 hours. Neurological evaluation was performed daily until discharge. On day 30 and 6 months after surgery all patients were seen at the outpatient clinic for neurological examination and assessment of mRS, NIHSS, Mini Mental Status (MMS), and the EORTC's QLQ-C30 questionnaire.[13] The answers from the QLQ-C30 were grouped according to symptoms and functioning, and used to obtain a summary surrogate parameter for quality of life.[14]

The mRS scores were assessed by independent trial nurses blinded to group assignment. Antiplatelet agents were restarted after 4 weeks and anticoagulants after 10 weeks if indicated, without prior imaging.

Management of recurrent CSH

The indication for surgery on recurrent or persisting CSH was based on imaging and clinical signs: if (i) patients showed symptoms or signs attributable to the mass effect of the hematoma or (ii) the CT-scan at 30 days showed persisting mass effect or midline shift (>50% of hematoma diameter or >50% midline shift compared to pre-operative values).

When neurological symptoms or signs persisted or occurred, emergency CT was performed irrespective of randomization assignment. If CSH with mass effect was diagnosed (>50% of hematoma diameter or >50% midline shift compared to pre-operative values), and clinical findings were compatible with it, the patient underwent re-operation.

In-house treatment costs and length of stay

To calculate the total costs from admission to the last follow-up visit, we reviewed all records of the hospital administration. Our calculation encompassed all costs for diagnostic procedures, treatment, and follow-up and expenditures incurred because of adverse events in our tertiary care hospital. The length of stay was measured by counting the number of days spent in our hospital and any medical institution the patient was transferred to, unless the patient returned to a nursing facility.

Statistics

For the calculation of the sample size of 368 patients we assumed a rate of good outcome (mRS 0–3) of 66% and 84% in the CT-arm and the no-CT-arm, respectively, and targeted by mistake a power of

97.5% (instead of 90%) leading to a sample size of 350 patients. We applied a 5% overhead to compensate for non-evaluable patients.[15]

The full analysis set included all patients who had consented and been randomized. This set was used for all efficacy and safety analyses. Missing data were not imputed, except for a sensitivity analysis of the primary endpoint where "poor outcome" was assumed for non-evaluable patients. The per-protocol (PP) population included all randomized patients analyzed according to day 2. It excluded patients who violated the imaging rules at day 30 and patients who prematurely withdrew from the study or were lost to follow-up. The PP population was used for a supportive analysis of the primary endpoint.

The primary analysis comparing the primary outcome in the two treatment arms made use of logistic regression including the stratification factor (pre-study anticoagulants or antiplatelet medication) with a supportive analysis based on the Cochran-Mantel-Haenszel (CMH) test stratified for the same factor. Homogeneity of treatment effect across potential risk factors was also assessed using logistic regression. Differences between the trial arms in terms of re-operations, safety parameters (death or predefined complications), death and complications were analyzed using Fisher's exact test. Count data, such as the number of surgeries on patients with recurrence of bleeding, were analyzed based on the Poisson distribution.

A Kaplan–Meier analysis was used for the time to first surgery for recurrence and the hazard ratio was computed based on Cox regression. Observations for event-free patients were censored at the time of last contact or consent withdrawal.

A logistic regression was applied to analyze risk factors for recurrence. The target variable was surgically treated recurrence of bleeding. Based on the literature, we identified anticoagulation, antiplatelet medication, arterial hypertension, and bilateral hematoma as risk factors for recurrence of bleeding, requiring surgical treatment.

All statistical tests were conducted at the two-sided 5% significance level and the level for all confidence intervals was 95% without adjustment for multiplicity.

After enrolment of 200 patients, we performed an interim analysis and decided to continue the study as planned.

RESULTS

Recruitment and follow-up

Patient enrollment, allocation, follow-up, and analysis are shown in Fig. 2. Six hundred and sixty-seven patients were screened between June 5, 2012 and August 1, 2016. Three hundred and sixty-one patients (54%) were randomized after written consent and available for full analysis, 181 in the CT-arm and 180 in the no-CT-arm. Table 1 shows the baseline characteristics of randomized patients. They were well balanced. The attrition rate was 4 patients (2%) in the CT-arm and 8 (4%) in the no-CT-arm. In total, mRS at 6 months was available for 349 patients, corresponding to 97% of the full analysis set. Up to month 6, brain imaging had been performed on 179 patients (98.9%) in the CT-arm and 71 patients (39.4%) in the no-CT-arm. CT-scans were missing for 4 patients (2.2%) in the CT-arm for day 2 and for 13 patients (7.2%) for day 30. In the no-CT-arm, CT was performed on 18 patients (10.6%) around day 2 and 16 patients (9.4%) around day 30, mostly because of a medical indication. The PP population consisted of 170 patients in the CT-arm and 168 in the no-CT-arm.

Primary endpoint

Fig. 3 shows the primary endpoint of favorable outcome (mRS of 0–3) at 6 months. Favorable outcome was similar in both arms and was reached by 160 (93%) patients in the no-CT-arm and 157 (89%) in the CT-arm (odds ratio 1.74; 95% CI 0.818–3.72; P=0.150). Results of the CMH test were in line with this finding (odds ratio 1.75; 95% CI 0.82–3.73). The between-arm difference for mRS was

not significant, either when treated as a categorical variable (P=0.793) or as a numerical variable (difference in means for CT – no-CT: 0.13, P=0.366, Wilcoxon rank-sum test). Supportive analyses with imputation of missing primary endpoint data as "poor outcome" did not show any significant difference (odds ratio 1.24; P=0.516 in the full analysis set and odds ratio 1.74; P=0.158 in the PP population) and were thus in line with the primary analysis. Post-hoc, we evaluated the homogeneity the of the randomized treatment effect as a function of the use of anticoagulants or antiplatelet agents prior to surgery, of age and of sex. In logistic regression models extending the one used for the primary analysis, only for age was the p-value for the test of the interaction with treatment smaller than 0.1 (0.06). In younger patients (age less than the median), the odds ratio for the treatment effect was 2.5 (95% CI: 0.48–13.7) but the overall rate of bad outcomes was very low (4%).

Secondary endpoints

Re-operation

After randomization, 98 surgeries for CSH were performed in 81 patients (Table 2). Sixty-seven patients underwent 1 additional surgery (19%), 11 underwent 2 (3.2%), and 3 had 3 interventions (0.8%).

We performed 59 surgeries (in 49 patients) for recurrent hematoma in the CT-arm, compared to 39 (in 34 patients) in the no-CT-arm (rate ratio 1.50; 95% CI 0.987–2.32). The Kaplan–Meier estimate of surgery probability was 27% for the CT-arm and 18.7% for the no-CT-arm (hazard ratio from Cox regression 0.665; 95% CI 0.427–1.04).

A logistic regression model assessing the probability of at least one surgical intervention for recurrent bleeding favored the no-CT-arm (odds ratio 0.612; 95% CI 0.369–1.02). The model included adjustments for pre-study anticoagulants or antiplatelet medication (associated with a decreased risk: odds ratio 0.51; 95% CI 0.303–0.891), arterial hypertension and bilateral hematoma. Forty of 59

patients with recurrent bleeding in the CT-arm (67.8%) and 38 of 39 in the no-CT-arm (97.4%) were clinically symptomatic.

Fig. 4 shows a Kaplan–Meier plot of survival without surgery for recurrent or persisting chronic subdural hematoma. Cumulative numbers of surgeries within 30 and 60 days were 39 and 54 in the CT-arm and 28 and 37 in the no-CT-arm. Overall, the majority took place within 30 days (68%), 25% within 2 months, and 7% more than 2 months after randomization. Patients in the CT-arm received 590 CT-scans during follow-up (mean: 3.26 per patient), compared to 204 in the no-CT-arm (mean: 1.13 per patient).

Safety

Twenty of the 361 patients (5.4%) died, 12 (6.7%) in the CT-arm and 8 (4.7%) in the no-CT-arm (rate ratio 1.49; 95% CI 0.561–4.21; Table 2).

There were 24 non-fatal complications, 14 in the CT-arm and 10 in the no-CT-arm (Table 2). We observed 88 predefined adverse events in the CT-arm and 59 in the no-CT-arm (rate ratio 1.48; 95% CI: 1.05–2.10).

NIHSS, MMS and quality of life

Baseline NIHSS and MMS were similar between trial arms (Table 1). After 6 months, median NIHSS scores were 0 in both arms (IQR 0–0; mean 0.27 and 0.26 in the CT and the no-CT-arm, respectively), and mean MMS 27.97 and 27.88 (median 29; IQR 27–30 for both arms). Mean quality-of-life score at 6 months was 55.04 and 55.41, for the CT and no-CT-arm, respectively (median 55.77 for both arms; IQR 53.85–56.73 [CT-arm] and 54.42–56.65 [no-CT-arm]).

Length of stay and costs

The number of days spent at a medical facility was similar in both trial arms (Table 2). Mean overall cost from hospital admission until the last follow-up visit was 21,298 Swiss francs (CHF) per patient in the CT-arm (median 16,038; IQR 12,530–24,716), and 18,047 CHF in the no-CT-arm (median 14,201; IQR 11,462–21,153). The difference in mean treatment costs of 3,251 CHF signifies 18% higher costs in the CT-arm compared to the no-CT-arm.

DISCUSSION

Routine CT-scans after surgical intervention for CSH failed to improve any measured outcomes. In addition, routinely scheduled CT-scans were associated with a trend toward more re-operations and increased morbidity and mortality. The presumption that routine CT-scans prior to hospital discharge and during follow-up would pick up clinically relevant CSH recurrence or persistence early on and would help to guide patient management was not confirmed. In fact, the opposite may be true. Unnecessary radiation exposure and extra expenses were incurred, recovery was no quicker, and morbidity and mortality of patients with CSH were not improved.

Recurrences and re-operations

The rate of recurrent or persisting CSH was 23%, similar to published findings.[4,16] Furthermore, we observed more additional surgeries in patients in the CT-arm than in the no-CT-arm (59 and 39, respectively) (Fig. 4). Management of clinically asymptomatic or improving patients might alter when CT is performed. Recurrent or persisting CSH in asymptomatic or improving patients are not detected without CT-scanning, and hence are not operated on. When CT is performed, however, treating physicians might consider re-operating on large, space-occupying hematomas even when clinically asymptomatic or improving. Nineteen of the 59 patients in the CT-arm who underwent re-operation were asymptomatic or improving when undergoing re-operation compared to only 1 of the 39 patients undergoing re-operation in the no-CT-arm. However, re-operations on symptomatic patients were similar in both trial arms: 40 patients in the CT-arm and 38 patients in the no-CT-arm.

Does follow-up with CT prevent detrimental outcome?

Concerns have been expressed that progressing recurrent hematoma in asymptomatic patients might be missed without CT imaging and patients could therefore be harmed or even die following

sudden clinical deterioration. However, none of the deaths in our trial was directly related to the CSH, and the death rate was similar in both trial arms (Table 2).

Complications

Re-operation for recurring CSH has previously been reported to increase the likelihood of adverse outcome including cognitive impairment, delirium, and death.[17] In our study, re-operation was recommended to all patients with a clinically symptomatic recurrence or persistence, regardless of which trial arm they had been allocated to. The number of re-operations, complications and adverse events in our patients was not statistically different between the trial arms, although nominally more frequent in the CT-arm than in the no-CT-arm.

CT-scans and costs

CT-scans remained a frequently used diagnostic tool in the no-CT arm as 39.4% of patients in the no-CT-arm received at least 1 follow-up scan because of new neurological deficits or lack of improvement after surgery. Nevertheless, the costs per patient in the CT-arm were higher than in the no-CT-arm by 3,251 CHF or 18%. This difference is too large to be directly attributed to imaging only (a CT-scan is billed at 320 CHF). Instead, the imaging strategy in the CT-arm probably increased the costs indirectly by triggering further follow-up visits, hospitalizations and surgeries.

Choosing wisely: Overuse of diagnostic tools may lead to overtreatment and to worse outcome

In our trial, routine CT-scans failed to improve any outcome measure. Rather, routine CT-scans seem to indicate overuse of diagnostic tools, potentially leading to overtreatment and worse outcomes. Based on our results, routine CT-scans after surgery on CSH are not indicated. CT should be restricted to patients with new or persisting neurological deficits. Furthermore, patients, their families, and

family physicians should be sensitized to the high rates of recurrent hematomas up to 2 months after surgery.

Limitations

TOSCAN was a single-center study and external validity is therefore limited. Adherence to the imaging protocol was good but not complete, and unplanned CT-scans were not indicated by independent physicians who were blinded to treatment assignment. This may have biased the study results to some extent. Finally, the cost analysis was performed retrospectively and underestimates total costs: it encompasses all costs incurred at our tertiary-care hospital for treatment and follow-up including treatment of complications, but it does not take into account any costs of treatment outside of our hospital, e.g., at rehabilitation facilities, other hospitals, family physicians, day-care, or nursing homes.

Conclusion

The randomized, controlled TOSCAN trial showed no benefit of routine follow-up CT-scans following surgery for CSH. Routine CT-scans did not improve clinical outcome. On the contrary, patients followed clinically without routine CT-scans had fewer re-operations and showed a tendency toward less morbidity and mortality. Performing follow-up CT-scans after evacuation of CSH only in patients with persisting or new neurological deficits appears to be a cost-effective and safe strategy to decrease morbidity, mortality, and unnecessary surgery.

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