Systematic Review

Title:

The use and impact of 12-lead electrocardiograms in acute stroke patients: A systematic review.

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Conflicts of Interest:

None declared

Abstract

Stroke is a leading cause of mortality and disability across the globe. Emergency Medical Services assess and transport a large number of these patients in the prehospital setting. Guidelines for UK ambulance services recommend recording a 12-lead electrocardiogram in the prehospital environment, providing this does not add to significant delay in transporting the patient to hospital, however this recommendation is not based on any evidence.

A systematic review was conducted to search and synthesise the literature surrounding the use of prehospital electrocardiograms in acute stroke patients, focusing on the prevalence of abnormalities and their association with prognosis and outcome.

Online databases, references from selected articles and hand searches were made to identify eligible studies. Two authors independently reviewed the studies to ensure eligibility criteria were met. Main outcomes were presence of abnormality on ECG, mortality and disability. No studies set in the prehospital environment were found by the search; therefore the eligibility

criteria were widened to include hospital-based studies. A total of 18 studies were subsequently included in the review.

Although the prevalence of ECG abnormalities appears common in hospitalised patients, their prognostic impact on mortality, disability and other adverse outcomes is conflicting amongst the literature.

There is a lack of research surrounding the use of prehospital ECG in acute stroke patients. Future studies should be based in the prehospital environment and should investigate whether undertaking an ECG in the prehospital setting affects clinical management decisions or has an association with mortality or morbidity.

Introduction

Stroke is a severe neurological disease, which can lead to death or serious disability. It has been estimated to be the second most common cause of death[1] and third most common cause of disability-adjusted-life years worldwide.[2] Emergency medical services (EMS) play a vital role in the recognition, assessment and transportation of stroke patients in the prehospital setting.[3]

Due to the nature of the disease the benefit of treatment is time-dependent.[4] For patients suffering acute ischaemic stroke rapid hospital admission and early intervention are essential to increase the chance of a positive outcome; therefore any unnecessary delay could be potentially harmful to the patient.

For EMS in the UK, the Joint Royal College Ambulance Liaison Committee (JRCALC)[5] guidelines recommend the clinician consider performing a 12-lead ECG, provided this does not result in a delay in transporting the patient to hospital.

The benefits of recording a pre-hospital ECG in patients with stroke are unknown, thus the recommendations are based on expert consensus rather than robust evidence.[6]

The objectives of this systematic review were to review systematically the literature surrounding the use and impact of prehospital ECGs in acute stroke patients, focusing on the prevalence of abnormalities and their effect on prognosis and outcome.

Methods

The review of this report were designed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and meta-Analyses) guidelines.[7]

Search Strategy/data sources

The electronic databases; Medline, psycINFO, CINAHL and the Cochrane database of systematic reviews were searched to retrieve relevant articles. The search strategy can be found as online supplemental material. The search was conducted on the 29/12/2013.

The reference lists of retrieved studies were searched. Hand-searches of key journals were conducted. Contact was made with experts and authors in this field and conference proceedings from Web of Science online database were searched in order to uncover any unpublished or grey literature.

Study selection

Titles and abstracts were screened independently by two reviewers (SM &

VK) in order to select potentially relevant studies, after which full texts were

obtained for further analysis as to whether they met the inclusion/exclusion

criteria (see below). Any discrepancies between the two reviewers were

resolved by discussion, with a third reviewer consulted if no agreement was

reached.

Relevant data were then extracted from the retrieved studies using a

customised data-extraction tool (see online supplemental material).

Inclusion Criteria

- Articles relating to the prevalence, detection and prognostic

  significance of ECG abnormalities taken in the prehospital environment

  from acute stroke patients. However, no prehospital studies were

  identified, therefore hospital based studies were included.

- Studies investigating ischaemic stroke and intracerebral haemorrhage,

  as well as transient ischaemic attacks.

- Articles published between 2003-2014, due to the possibility that not all

  ambulances may have been equipped with ECG monitoring devices

  prior to 2003.

Exclusion Criteria

- Studies investigating implantable cardiac monitoring devices.

- Studies investigating subarachnoid haemorrhage.

- Studies investigating continuous, delayed or extended monitoring.

- Non-English language articles.

- Non-human studies.

- Opinion articles/editorials and case reports.

Results

The search strategy yielded 18 relevant articles that were included in the review. The articles were grouped into three themes (figure 1). Due to the heterogeneity of the designs, population groups and outcomes measured, it was deemed not feasible to undertake a meta-analysis.

Insert Figure 1.

Non-specific ECG abnormalities in stroke patients

A total of seven articles were found to investigate non-specific ECG abnormalities in stroke patients.

Insert Table 1

Insert Table 2

When comparing prevalence of ECG abnormalities in subtype of stroke, AF, non-specific T wave abnormality and T-wave inversion are shown to have a

significant association with ischaemic stroke, while sinus tachycardia and ectopic beats >10% show an association with intracerebral haemorrhage (Table 1).

ST-T changes were found to have an association with mortality across the different subtypes of stroke.[8,9] ST-T changes were also found to be associated with other outcomes such as elevated levels of TnT [10] and NT-proBNP (β =76.5, p=0.011).[11]

QTc prolongation was reported to have an association with involvement of the insular cortex (OR 10.9, 95% CI 1.0-114.6) as well as presence of intraventricular blood and hydrocephalus on admission CT scan (10.8, 95% CI 1.6-70.9).[12]

Atrial fibrillation was reported to have an association with 3-month mortality in ischaemic stroke patients (OR 2.0, 95% CI 1.3-3.1).[9] There was also an association with mortality and the presence of a Q wave in two or more leads[13] (HR of mortality 3.42, 95% CI 1.43-8.19; p=0.013).

Sinus tachycardia (OR 4.8, 95% CI 1.7-14.0), ST depression (OR 5.3, 95%CI 1.1-24.9) and inverted T-waves (OR 5.2, 95% CI 1.2-22.5) predicted mortality at 3-months in intracerebral haemorrhage patients.[9]

Belvis et al. found no characteristic ECG pattern to identify patients with cryptogenic stroke.[14]

Insular Cortex

The insular cortex has been hypothesised to play an important role in the occurrence of ECG abnormalities following acute stroke, due to disturbance of sympathetic and parasympathetic tone, the interconnections with subcortical autonomic centres, limbic system and hypothalamus and the release of catecholamines causing myocardial damage.[15–17]

This group of literature provides conflicting results as to whether insular infarcts are associated with ECG abnormalities. Pasquini et al.[18] results showed that there was no statistically significant difference in terms of ECG variables between patients with and without recent insular infarcts, as well as no difference between patients with right or left insular involvement.

The remaining studies found insular lesions associated with sinus tachycardia (>120bpm) (p=0.001), ectopic beats >10% (p=0.032), ST elevation (p=0.011).[19] Prolonged QTc and LBBB were independent predictors of all-cause mortality at 2 years in patients with right insular involvement.[20]

After combining the results from each of the studies, this review found no ECG abnormality to be significantly associated with insular involvement or no insular involvement, however due to the small numbers involved these results should be interpreted with caution (see online supplemental material).

QTc and QTd

The final theme presented in this review focuses on literature examining the relationship between acute stroke and the presence of prolonged QT intervals corrected for heart rate (QTc)[21–24] and QT dispersion (QTd).[25–28]

Insert Table 3

While QTc prolongation was shown to be associated with mortality up to approximately 90 days by two studies,[23,24] Wong et al.[22] reported an association between QTc prolongation and total mortality up to 5 years (RR 2.9; 95% CI 1.6-5.3, p<0.001). While Stead et al.[23] limited their follow-up to 90 days, Hjalmarsson et al.[24] continued for 12-months, but still found no association past the 90-day point (OR 0.90; 95% CI 0.42-1.97, p=0.800).

Lazar et al.[29] found that patients who died had a greater QTd compared with those that survived (44±26ms vs 2±21, p<0.001). A positive correlation was also found between National Institute of Health Stroke Scale (NIHSS) and QTd (r=0.57, p<0.001).

Afsar et al.[25] found that while QTd is increased in the first 24-hours following stroke, the case and control groups presented with similar QTd measurements in the 72-hour ECG. Another study reported QTd was longer in patients that had suffered an acute ischaemic stroke, compared with controls (QTd 60.6±25.1 ms vs 48.8±13.2 ms, p=0.03).[26]

The results of one study showed that compared with the most recent pre-stroke ECG available, a statistically non-significant mean increase of 4.1ms (p=0.14) in QTd was found following acute stroke, with no relationship with stroke subtype or location of stroke.[28]

Discussion

This review set out to investigate the prevalence and prognostic significance of ECG abnormalities found in prehospital stroke patients. The literature search identified no relevant studies based in the prehospital setting.

It is still unclear whether there is any discernable value of conducting an ECG in stroke patients presenting to EMS. The UK guidelines do not provide an evidence-based reasoning behind their recommendation, nor has this review found any such evidence to back up the recommendation. The potential benefit or harm as a result of time delays from conducting the procedure in this population of patients is unknown due to the lack of evidence.

This review recommends that a study be performed in order to answer the following question;

In acute stroke patients assisted in the prehospital environment, is having a 12-lead ECG, compared with no 12-lead ECG associated with treatment decisions and outcome?

While it was clear that ECG abnormalities are prevalent amongst hospitalised patients, the frequency and prognostic impact on different outcomes vary amongst the available literature. Methodological limitations and heterogeneity in study outcome and design made comparison between results difficult; therefore it is not possible to draw firm conclusions.

A limitation to many of the studies in this review included the use of small samples and single centred, retrospective studies. Well-conducted, larger, multi-centered experimental studies could produce more precise results. Many studies do not report confidence intervals, providing only descriptive statistical results.

Lack of reporting of basic information such as sampling methods, inclusion/exclusion criteria, definition of variables and potential confounding factors was common amongst the studies, leaving ambiguity over the strengths and limitations. Following reporting criteria, such as the STROBE (Strengthening the reporting of observational studies in epidemiology) statement[30] would increase the transparency of the research.

Different outcome measurement tools were used among the studies, such as the modified Rankin scale (mRS), Glasgow outcome scale (GOS) and the Barthel index. Using one or a standardised set of validated tools would allow easier comparison between the studies.[31]

The limitations of this review include the exclusion of non-English language papers, as some relevant articles may have been overlooked. The heterogeneity of the studies included in the review meant that a meta-analyses was not able to be performed. There is a strong risk of bias in many of the studies due to missing data, lack of blinding and not adjusting for potential confounders.

Conclusion

There is heterogeneity of research design and outcomes measured and in the existing body of hospital-based literature. Although the prevalence of ECG abnormalities in the hospital environment appears to be common, the prognostic impact on mortality, disability and other adverse outcomes is disputed. Due to the variable quality of the studies in this review, no firm conclusions can be drawn.

There is a paucity of research investigating the use and impact of recording 12-lead ECGs in acute stroke patients in the prehospital environment. Future studies should evaluate whether this assessment adds to patient management or outcome and whether it should be routinely advised in this population of patients.

Conflicts of interest

None declared

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Table 1. *Prevalence of ECG abnormalities across stroke subtypes*

ECG abnormality	Ischaemic stroke N=1645 (%)	ICH N=186 (%)	χ^2=* (Fisher's exact where cell frequencies <10)
Sinus tachycardia	168 (10%)	34 (18%)	0.002
Sinus bradycardia	95 (6%)	20 (11%)	0.008
AF and atrial flutter	239 (15%)	7 (4%)	0.000
NSSTT changes	113 (7%)	7 (4%)	0.105
ST elevation	41 (2%)	10 (5%)	0.023
ST depression	239 (15%)	14 (8%)	0.009
NST abnormality	81 (5%)	0 (0%)	0.002
T-wave inversion	220 (13%)	8 (10%)	0.000
QTc prolongation	167 (10%)	20 (11%)	0.798
Q wave	31 (2%)	4 (2%)	0.802
LVH	0 (0%)	5 (3%)	-
A-V block	148 (9%)	15 (8%)	0.672
RBBB	20 (1%)	0 (0%)	0.131
LBBB	3 (0.2%)	0 (0%)	-
Ventricular tachycardia >5s	8 (0.5%)	0 (0%)	0.341
Ectopic beats >10%	214 (13%)	44 (24%)	0.000

ICH= Intracerebral haemorrhage, LBBB= Left bundle branch block, AF=Atrial fibrillation, RBBB= right bundle branch block, SVT= supraventricular tachycardia, NSVT= nonsustained ventricular tachycardia, AV block= atrioventricular block of any kind, LVH= left ventricular hypertrophy, NST abnormality = non-specific T wave abnormality, NSSTT= non-specific ST-T wave abnormality,
*Significance level = 0.003
Where cell counts <5 statistical tests not conducted

Table 2. *Studies investigating non-specific ECG abnormalities in stroke patients*

Authors	Sample size	Design	Type of stroke	Findings
Dogan et al.[8]	162	Prospective cohort	Ischaemic stroke	ST-segment change associated with 4-week mortality (OR 2.6; 95% CI 1.3-5.6, p=0.01)
Tanaka et al.[13]	216	Prospective cohort	Ischaemic stroke	The presence of Q-waves in more than two leads was independently associated with death after stroke (HR of mortality 2.75; 95% CI 1.23-6.14, p=0.013)
Christensen et al.[9]	692	Retrospective cohort	Ischaemic stroke	3-month mortality was predicted by AF (OR 2.0; 95% CI 1.3-3.1), atrioventricular block (OR 1.9; 95% CI 1.2-3.9), ST elevation (OR 2.8; 95% CI 1.3-6.3), ST depression (OR 2.5; 95% CI 1.5-4.3) and inverted T-waves (OR 2.7; 95% CI 1.6-4.6).
Fure et al.[10]	279	Prospective cohort	Ischaemic stroke	ST depression (OR 0.31; 95% CI 0.13-0.73, p=0.008) and Q waves (OR 0.36; 95% CI 0.14-0.93, p=0.035) were significantly associated with rise in TnT.
Belvis et al.[14]	104	Prospective cohort	Ischaemic stroke	There is no characteristic ECG pattern to identify patients with cryptogenic stroke.
Jensen et al.[11]	192	Prospective cohort	Ischaemic stroke	ST-T changes were associated with increased levels of NT-proBNP (β= 76.5, p=0.011)
Christensen et al.[9]	155	Retrospective cohort	ICH	Sinus tachycardia (OR 4.8; 95% CI 1.7-14.0), ST depression (OR 5.2; 95% CI 1.1-24.9) and inverted T wave (OR 5.2; (95% CI 1.2-22.5) predicted 3-month mortality
Van Bree et al.[12]	31	Retrospective cohort	ICH	QTc prolongation was associated with ICH involvement of the insular cortex (OR 10.9; 95% CI 1.0-114.6) and presence of intraventricular blood and hydrocephalus on admission CT (OR 10.8; 95% CI 1.6-70.9)

ICH= intracerebral haemorrhage, OR= odds ratio, CI= confidence interval, HR= hazards ratio, VA= ventricular

arrhythmia

Table 3. *Studies investigating QTc/QTd*

Authors	Sample size	Design	Type of stroke	QTc/QTd	Findings
Wong et al.[21]	404	Prospective cohort	Not stated	QTc	Prolonged QTc in lead V6 was associated with cardiac death (Relative risk 2.8; 95% CI 1.1-7.3, p=0.028) and death of any cause (relative risk 2.9; 95% CI 1.6-5.3, p<0.001). If QTc in V6 exceeded 480ms, the specificity of predicting cardiac death within 5 years after stroke was 94%
Wong et al.[22]	202	Prospective cohort	82% infarct, 18% bleeds, 36% TIA	QTc	Prolonged QTc max significantly correlated with increasing blood pressure (systolic BP correlation coefficient 0.27, p<0.001), left ventricular mass index (correlation coefficient 0.26, p=0.002) and depressed heart rate variability (standard deviation of normal to normal RR intervals (SDNN) correlation coefficient -0.30, p<0.001).
Stead et al.[23]	345	Prospective cohort	Ischaemic stroke	QTc	Patients with prolonged QTc were more likely to die within 90 days compared with patients without (RR 2.5; 95% CI 1.5-4.1, p<0.001). The identified cutoffs for increased risk of death at 90 days were 440ms for women and 438ms for men.
Hjalmarsson et al.[24]	478	Prospective cohort	432 Ischaemic, 46 intracerebral harmoeehage	QTc	Prolonged QTc (≥450ms) was a predictor for mortality during first three months following stroke (OR 8.88; 95% CI 1.98-9.59, p=0.05)
Afsar et al.[25]	36	Prospective	30 Ischaemic 6 Haemorrhagic	QTd	In 24-hour ECG, corrected QTd was significantly greater in patients with large infarcts and large haemorrhages (mean [SD] 70 [20] vs 51 [20]ms, p<0.05)
Familoni et al.[26]	60	Case-control	Not stated	QTd	QTd was greater in cases than in controls (60.6±25.1 ms vs. 48.8±13.2 ms, p=0.03)
Lazar et al.[27]	30	Retrospective cohort	Ischaemic	QTd	QTd was higher in patients who died in comparison with survivors (44±26 ms vs. -2±21 ms, p<0.001). NIHSS correlated directly with QTd (r=0.57, p<0.001).
Mulcahy et al.[28]	45	Retrospective cohort	Ischaemic	QTd	QTd increased by 4.1ms after stroke, however this change was not statistically significant (95% CI -1.3-9.5, p=0.14)

Fig 1 *PRISMA flowchart of the literature search*

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│ 76,757 records identified     │  ────────────────▶ │ 27,409 non-human         │
│ through online databases      │                    │ articles excluded        │
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│ 49,348 articles identified    │  ────────────────▶ │ 10,981 non-English-      │
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│ 38,367 articles identified    │  ────────────────▶ │ 17,919 articles >10      │
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│ 20,448 relevant articles      │  ────────────────▶ │ 20,432 irrelevant/       │
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| Non-specific ECG abnormalities in stroke patients n=7 | Insular involvement affecting ECG abnormalities in stroke patients n=3 | Impact of QTc and QTd on stroke patients n= 8 |