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Review

Double sequential external defibrillation for refractory ventricular fibrillation out-of-hospital cardiac arrest: A systematic review and meta-analysis

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Abstract

Background: Double sequential external defibrillation (DSED) is a novel intervention which has shown potential in the management of refractory ventricular fibrillation (VF). This review aims to identify the literature surrounding the use of DSED in out-of-hospital refractory VF and assess whether this intervention improves survival outcomes.

Methods: The databases Ovid Medline, EMBASE, CINAHL, SCOPUS and the Cochrane Library were searched from their commencement to January 29th 2018. Google (scholar) was also searched for grey literature. We combined MeSH terms and text words for DSED in refractory VF and included studies that used an interventional or observational design. Study quality was assessed using the Newcastle-Ottawa Scale. A random effects model using the DerSimonian & Laird method was used to calculate pooled ORs and 95% CIs.

Results: The search yielded 5351 unique records, of which two retrospective studies met the eligibility criteria. No randomised controlled trials were identified. The pooled population included 499 patients of which 19% (n = 95) received DSED and 81% (n = 404) were managed with standard resuscitation protocols. Confirmation of DSED was self-reported by paramedics. Neither study adjusted for confounding factors or baseline characteristics across the study groups. The definition of refractory VF and the protocol for DSED use differed across studies. Over half of cases were witnessed cardiac arrests (58.7%, n = 293) and bystander CPR was initiated in 53.3% (n = 266) of cases. In the meta-analysis, DSED had no effect on survival to hospital discharge (OR 0.69, 95% CI: 0.30, 1.60), event survival (OR 0.98, CI: 0.59, 1.62) or ROSC (OR 0.86, 95% CI: 0.49–1.48).

Conclusion: The effectiveness of DSED remains unclear. Further well-designed prospective studies are needed to determine whether DSED has a role in the treatment of refractory VF.

Keywords: Out-of-hospital cardiac arrest, Defibrillation, Double sequential external defibrillation, Ventricular fibrillation, Resuscitation, Emergency medical services

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Introduction

Out-of-hospital cardiac arrest (OHCA) remains a common cause of death and is estimated to affect as many as five million people worldwide every year.[1] Although overall survival from OHCA remains low, patients who present to emergency medical services (EMS) with initial ventricular fibrillation (VF) have the highest likelihood of neurologically intact survival.[2,3] In fact, the vast majority of VF episodes are treatable in the field with as many as 70% achieving sustained return of spontaneous circulation (ROSC) on hospital admission.[4]

However, there are a subset of patients with VF who remain refractory to treatment, despite repeated administration of defibrillation, adrenaline (epinephrine) and anti-arrhythmic drugs.[5] Although a standard definition for refractory VF is yet to be established, some studies report refractory VF as three or more sustained episodes of VF,[6] while others define refractory VF as a failure of five defibrillation attempts.[7] If refractory VF is not treated promptly it can have a mortality rate as high as 97%.[8] Existing approaches to treatment include extracorporeal membrane oxygenation (ECMO) or beta-blockers for sympathetic control, although the efficacy of these interventions remain unclear and long delays before their use may also lead to poorer outcomes.[9,10]

Double sequential external defibrillation (DSED) is a novel intervention which has shown potential in the management of refractory VF.[7,11] DSED works by utilising two defibrillators and two pairs of electrodes on the same patient to deliver two shocks in close succession. It is easy to apply and can be used in the out-of-hospital setting. This could result in fewer delays to successful cardioversion compared to other interventions. Over the last decade, a series of case reports involving OHCA patients have reported successful reversion of refractory VF with DSED.[11–15] However, the effectiveness of DSED in refractory VF is limited due to the lack of uniform data.

This systematic review aims to identify the relevant literature surrounding the use of DSED in out-of-hospital refractory VF and assess whether this intervention improves survival to hospital discharge.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-Analysis of Observational Studies in Epidemiology.[16,17] The systematic review protocol was registered prior to commencement of the study (Prospero #CRD42017072789).

Data sources and search strategy

The databases EMBASE, Ovid Medline, CINAHL, SCOPUS, and the Cochrane Library were searched from their commencement to January 2018. A combination of subject headings and key words relevant to DSED and refractory OHCA were combined using Boolean terms as appropriate. The search strategy included: [(refractory ventricular fibrillation OR resuscitat$ OR cardiac arrest$ OR ventricular fibrillation OR vf) AND (dual$ OR double$ OR sequen$ OR syncroni$ OR defibrillation$ OR shock$)]. In addition, a search of the grey literature was conducted using Google Scholar and the reference lists of relevant papers were hand-searched to identify further studies that might have been missed by the electronic search.

Study selection and eligibility

The titles and abstracts of relevant studies were appraised for eligibility by two authors (AD and ZN) independently. The abstracts of the selected titles were read, and full texts were sourced and reviewed for those studies which were considered potentially relevant. Studies were eligible for inclusion if they: (1) compared the use of DSED with standard defibrillation in OHCA patients with refractory VF, (2) reported on adults greater than 18 years, (3) reported at least one of the following outcome measures: survival to hospital discharge, neurologically intact survival, 30-day survival, event survival, prehospital ROSC or successful cardioversion, and; (4) used an interventional or observational design. Articles were excluded if they were case reports, case series, letters, opinions or animal studies. Articles not written in English or published prior to the last 30 years were also excluded from the analysis. Any discrepancies between the two reviewers were resolved through consensus.

Data extraction and quality assessment

Two authors (AD and ZN) independently extracted study information and performed quality assessments. A standardised data extraction form was developed with the following study variables: setting, study location, number of participants, demographic characteristics, resuscitation protocol used, definition of refractory VF, number of shocks delivered, and adjusted effect sizes (with 95% confidence intervals [CIs]) for all relevant outcome measures. If an adjusted effect estimate for DSED was not available, an unadjusted estimate was used in the quantitative data synthesis. If more than one effect estimate was provided in the study, we recorded the estimate adjusted for the largest number of confounders.

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which rates the quality of observational studies using three domains, including selection, comparability, and outcome.[18] If there was insufficient information in the published article to conduct the data extraction or quality assessment, we made attempts to contact the authors for further clarification.

Data synthesis

The primary outcome of the study was survival to hospital discharge. Secondary outcomes included neurologically intact survival, 30-day survival, event survival, prehospital ROSC and successful cardioversion. Differences in study outcomes between patients receiving DSED and standard defibrillation are reported as odds ratios (OR) with 95% CI. A random effects model using the DerSimonian & Laird method was used to calculate pooled ORs and 95% CIs. A random effects model was used to allow for differences in the intervention effect across the included studies. Heterogeneity was quantified using the I^2 statistic. We performed sensitivity analyses excluding patients who were identified in one study to have recurrent VF. Meta-analysis was performed using STATA Statistical Software version 14.0. All statistical tests used a two-sided p-value <0.05.

Results

Study selection

The study selection flow-chart is shown in Fig. 1. The search strategy yielded 5351 non-duplicate titles, of which 20 were

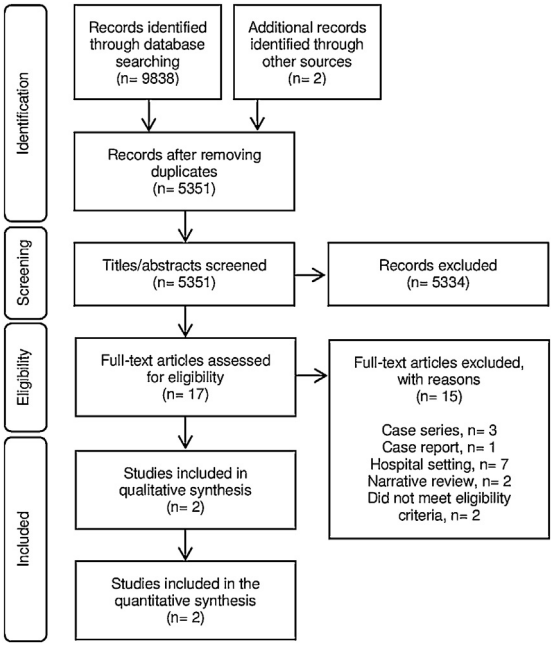

Fig. 1 – Study selection flow-chart.

considered potentially relevant to the study. After screening the abstracts, 17 articles were retrieved in full-text and assessed for eligibility. Of these, two studies met the eligibility criteria. Four case series involving DSED applied in the prehospital setting for OHCA were not included in the review, and are described in Table 1.

Study characteristics

The characteristics of the two included studies are shown in Table 2. No randomised trials were identified. Both studies were observational and retrospective in design. One study was conducted in London, England, the other from Texas, United States. The pooled population included 499 patients of which 19% (n = 95) received DSED and 81% (n = 404) did not receive DSED. Most patients were male (78.6%, n = 392) and over half of cases were witnessed cardiac arrests (58.7%, n = 293). Bystander CPR was initiated in 53.3% (n = 266) of cases. Only one study reported the number of cases presenting with initial shockable rhythms.

Quality assessment and publication bias

Study quality assessment (Newcastle-Ottawa Scale score) is shown in Table 2. Both studies had significant issues with methodological quality and neither study adjusted for confounding factors or baseline characteristics across the study groups. Missing data occurred in eight percent of the population in the Ross et al. study and four percent of patients were lost to follow up in the Emmerson et al study. Sample sizes were small and confirmation of DSED was self-reported by the paramedics in both studies rather than confirmation using defibrillator print-outs.

Ross et al. included a control group from the same population, while Emmerson et al. used a similar group of matched controls. The

Table 1 – Case series describing the use of DSED in the prehospital setting on OHCA patients (not included in the systematic review).

Author (year)	Year of publication	Location	Participants	Indication for DSED	Termination of VF	Prehospital ROSC	Survived to discharge
Cabanas et al.[13]	2015	North Carolina, USA	10 adult OHCA patients, 6 of which presented with an initial shockable rhythm.	Persistent VF following at least five single defibrillation attempts and a single dose of antiarrhythmic medication. DSED applied prehospital.	7 (70%)	3 (30%)	0
Cortez et al.[15]	2016	Ohio, USA	12 adult OHCA patients, 11 of which presented with an initial shockable rhythm.	Persistent VF following at least five single defibrillation attempts. DSED applied prehospital.	9 (75%)	3 (25%)	3 (25%)
Johnston et al.[14]	2016	Ontario, Canada	A 28-year-old who sustained a bystander witnessed VF OHCA.	Persistent VF after six single defibrillation attempts, administration of epinephrine, and two doses of the study drug used in the ALPS trial. DSED applied prehospital.	1 (100%)	1 (100%)	1 (100%)
Merlin et al.[11]	2016	New Jersey, USA	7 adult OHCA patients. Initial recorded arrest rhythms were not reported.	Persistent VF following at least three single defibrillation attempts, epinephrine administration and a single dose of antiarrhythmic medication. DSED applied prehospital.	5 (71%)	4 (57%)	3 (43%)

DSED denotes double sequential external defibrillation, OHCA out-of-hospital cardiac arrest, VF ventricular fibrillation. ALPS Amiodarone Lidocaine Placebo Study, ROSC return of spontaneous circulation.

Table 2 – Characteristics of studies included in the systematic review and meta-analysis.

Author	Year of publication	Location	Study design	Participants	Indication for DSED	Received DSED	Overall survival to discharge	Study quality assessment (NOS Score)
Ross et al.[19]	2016	Texas, USA	Retrospective, observational	279 OHCA patients with either DSED applied or at least four single defibrillation attempts for recurrent/refractory VF. Initial recorded rhythms not reported.	Persisting VF after three unsuccessful defibrillation attempts. Multiple DSED attempts permitted.	50 (18%)	37 (13%)	3/9
Emmerson et al.[6]	2016	London, UK	Retrospective, observational	220 OHCA patients with either DSED applied or more than six consecutive unsuccessful standard defibrillation attempts. The initial recorded arrest rhythm was shockable in 182 (83%) patients.	Persisting VF after six unsuccessful defibrillation attempts (including three in the anterior-posterior position), followed by a single dose of anti-arrhythmic medication. Multiple DSED attempts permitted.	45 (20%)	14 (7%)	3/9

DSED denotes double sequential external defibrillation, OHCA out-of-hospital cardiac arrest, VF ventricular fibrillation. NOS Newcastle-Ottawa Scale.

threshold for DSED differed between the two studies. Ross et al. allowed DSED following three conventional defibrillations at 200 joules, however this was left to the discretion of the lead paramedic. In contrast, a total of six-shocks were administered prior to DSED according to the protocol by Emmerson et al., three conventional shocks and three with the defibrillation pads in the anterior-posterior position. Ross et al. included patients with recurrent VF and refractory VF and then conducted a sub-analysis excluding the refractory VF cohort (26 of 50 patients). In contrast, Emmerson et al. attempted to exclude patients who had recurrent VF, however defibrillator downloads were not available at the time, thus some cases of recurrent VF may have been included.

Quantitative data synthesis

Both studies reported on survival to hospital discharge, event survival and return of spontaneous circulation (ROSC). No study reported on neurologically intact survival, 30-day survival, or successful cardioversion. For all outcomes, only unadjusted ORs were reported. The results of the quantitative data synthesis are shown in Fig. 2. DSED had no effect on survival to hospital discharge (OR 0.69, 95% CI: 0.30, 1.60; Fig. 2a), event survival (OR 0.98, CI: 0.59, 1.62; Fig. 2b) or ROSC (OR 0.86, 95% CI: 0.49–1.48; Fig. 2c). There was no significant evidence of heterogeneity detected in any outcome. In a sensitivity analysis, we excluded patients described by Ross et al. as experiencing recurrent, but not refractory VF. In these analyses, the pooled estimates remained unchanged for survival to hospital discharge (OR 0.90, 95% CI: 0.36, 2.24), event survival (OR 1.16, 95% CI: 0.65, 2.07) and ROSC (OR 0.81, 95% CI: 0.36, 1.79).

Discussion

This systematic review identified only two small retrospective observational studies involving DSED in refractory VF during OHCA.[6,19] Our quantitative data synthesis suggests that DSED has no effect on survival to hospital discharge or pre-hospital outcomes. However, these results should be interpreted in the context of the limitations of the individual studies included in this systematic review. Only two studies were eligible for the review, neither of which were randomised controlled trials. Both were retrospective in nature with significant methodological issues including small sample sizes and risk of bias. Although no statistical heterogeneity was identified, the methodologies are clinically different. Finally, a standard definition for refractory VF and treatment protocol for DSED was not uniform across the included studies.

Currently, there is no standard approach for when DSED should be applied to a patient who remains in refractory VF. Small case series and case reports describe inconsistent approaches,[1,13–15] varying from 10 to 51 min of unsuccessful resuscitation or three to 18 unsuccessful standard shocks.[11,13–15] Despite these differences, these studies reported instances of successful reversion of refractory VF and survival to hospital discharge when DSED was utilised. However, when applied in consecutive patients the outcomes reported in these case series are not consistent with the findings of this review.[6,19]

Similarly, there were differences in the application of DSED between both studies included in this systematic review. In the protocol described by Ross et al., DSED could be utilised following three conventional defibrillations at 200 joules, however the exact number of standard defibrillation attempts before DSED was not reported.[19] In contrast, Emmerson et al. reported a protocol of DSED to follow six standard shocks.[6] However, the mean number of standard defibrillation shocks for patients who received DSED was 14, compared to 10 shocks delivered to the standard defibrillation group.[6] Furthermore, in Emmerson's study only specialist paramedics were authorised to deliver DSED during resuscitation efforts which may introduce treatment bias.[6] In addition, an increased number of shocks also indicates longer down times, which may have also worsened outcomes in patients receiving DSED.[20] Finally, the amount of energy delivered during DSED also varied between the two studies.

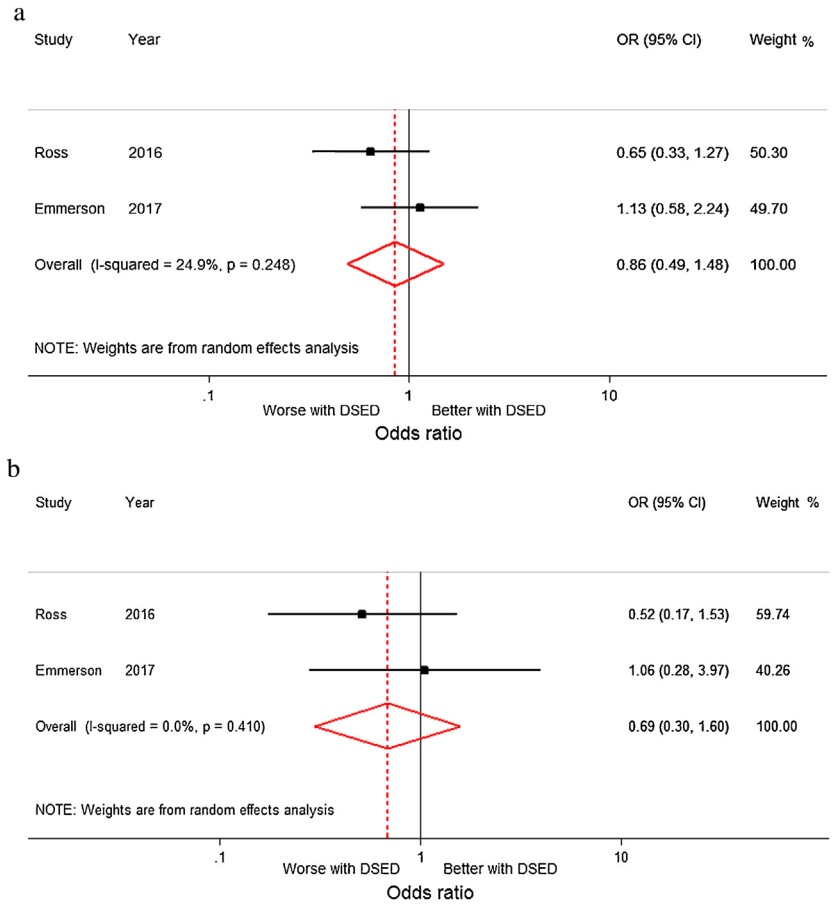

Fig. 2 – a) Meta-analysis of studies reporting the impact of DSED on survival to hospital discharge. b) Meta-analysis of studies reporting the impact of DSED on event survival. c) Meta-analysis of studies reporting the impact of DSED on return of spontaneous circulation.

Although there were no significant differences in the unadjusted rate of survival to hospital discharge, event survival and ROSC, neither study made attempts to adjust for baseline characteristics. This is partly due to their small sample size and lack of variability in baseline factors. However, Emmerson's study did have a higher proportion of witnessed cardiac arrest in the standard defibrillation cohort compared to the DSED cohort.[6] Bystander-witnessed arrests are associated with an increase in survival, thus group selection may have inadvertently favoured the standard defibrillation group.[21]

Both the safety and efficacy of DSED have been questioned in medical literature. Although there are multiple case reports describing remarkable success with the use of DSED, its exact mechanism for terminating refractory VF over standard defibrillation approaches remains unclear. Different hypotheses have been reported, including a larger current being enough to overcome the fibrillation,[22,23] delivering sequential shocks lowering the defibrillation threshold,[11,24] and alternating the vector of electricity across the myocardium depolarising a higher proportion of tissue.[11,25] There is also concern that application of dual shocks in close succession may lead to catastrophic defibrillator damage/failure though this had not been described until recently.[26] These issues raise further questions about the feasibility of using DSED in clinical practice.

Limitations

Our systematic review is limited by the methodological quality of included studies. Importantly, we did not find any randomised controlled trials comparing DSED to standard defibrillation for patients in refractory VF. The two small observational studies included in this meta-analysis are limited by methodological issues, including an imbalance in baseline characteristics between treatment groups and the potential for bias. In addition, despite our broad review of the peer-reviewed and grey literature, it is possible that some studies may have been missed.

Conclusion

This systematic review comparing DSED with standard defibrillation did not find any evidence that DSED was associated with an improvement in survival outcomes for patients with refractory VF OHCA. Our results are limited by the methodological quality of included studies, high risk of bias, small sample sizes and a lack of robust clinical trials. As such, the routine use of DSED cannot be recommended in patients with refractory VF. Further well designed prospective studies are needed to assess the efficacy and safety of this intervention for OHCA patients who are refractory to conventional treatment.

Conflicts of interest

None declared.

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