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Review

Double (dual) sequential defibrillation for refractory ventricular fibrillation cardiac arrest: A systematic review

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Abstract

Introduction: Cardiac arrests associated with shockable rhythms such as ventricular fibrillation or pulseless VT (VF/pVT) are associated with improved outcomes from cardiac arrest. The more defibrillation attempts required to terminate VF/pVT, the lower the survival. Double sequential defibrillation (DSD) has been used for refractory VF/pVT cardiac arrest despite limited evidence examining this practice. We performed a systematic review to summarize the evidence related to the use of DSD during cardiac arrest.

Methods: This review was performed according to PRISMA and registered on PROSPERO (ID: CRD42020152575). We searched Embase, Pubmed, and the Cochrane library from inception to 28 February 2020. We included adult patients with VF/pVT in any setting. We excluded case studies, case series with less than five patients, conference abstracts, simulation studies, and protocols for clinical trials. We predefined our outcomes of interest as neurological outcome, survival to hospital discharge, survival to hospital admission, return of spontaneous circulation (ROSC), and termination of VF/pVT. Risk of bias was examined using ROBINS-I or ROB-2 and certainty of studies were reported according to GRADE methodology.

Results: Overall, 314 studies were identified during the initial search. One hundred and thirty studies were screened during title and abstract stage and 10 studies underwent full manuscript screening, nine included in the final analysis. Included studies were cohort studies ($n = 4$), case series ($n = 3$), case-control study ($n = 1$) and a prospective pilot clinical trial ($n-1$). All studies were considered to have serious or critical risk of bias and no meta-analysis was performed. Overall, we did not find any differences in terms of neurological outcome, survival to hospital discharge, survival to hospital admission, ROSC, or termination of VF/pVT between DSD and a standard defibrillation strategy.

Conclusion: The use of double sequential defibrillation was not associated with improved outcomes from out-of-hospital cardiac arrest, however the current literature has a number of limitations to interpretation. Further high-quality evidence is needed to answer this important question.

Keywords: Out-of-hospital cardiac arrest, Cardiopulmonary resuscitation, Emergency medical services, Ventricular fibrillation, Double sequential defibrillation

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Introduction

Cardiac arrest patients with initial ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) have a higher probability of survival compared with patients with an initial non-shockable rhythm.[1] Treatment of VF/pVT includes high-quality cardiopulmonary resuscitation (CPR) and defibrillation, with the time to defibrillation being a major determinant of treatment success.[2,3] Ten to 20% of patients in a shockable rhythm do not respond to initial defibrillation and antiarrhythmic medications [4,5] and are considered to be in refractory VF/pVT. In these patients, an increased number of defibrillation attempts is associated with worse outcomes.[6]

Double (or dual) sequential defibrillation (DSD) has gained popularity as an alternative treatment option for patients who fail to respond to standard defibrillation attempts. Double sequential defibrillation uses two defibrillators; the first with defibrillation pads in the anterior–lateral position, and the second with pads in the anterior-posterior or adjacent antero-lateral positions. Two defibrillatory shocks are given in rapid succession; the operator either aiming to deliver both shocks at the same time, or deliberately introducing a brief pause between the two. The proposed mechanisms for DSD include an alternative energy vector, increased energy dose, defibrillation of a greater critical mass, or the timing between sequential defibrillations lowering the impedance threshold.[7,8]

Despite the increasing popularity, there is limited evidence for the effectiveness of DSD for refractory VF/pVT. A recent meta-analysis performed in 2019 concluded that the effectiveness of DSD remained unclear and further well-designed prospective studies were needed to determine whether DSED has a role in the treatment of refractory VF.[9] Since this meta-analysis, several other studies have been published which have contributed significantly to the available outcome data for DSD. Our objective was to therefore conduct a systematic review incorporating these new studies to examine current evidence for the effectiveness of DSD for the treatment of refractory VF/pVT cardiac arrest.

Methods

We conducted a systematic review to collect and examine evidence related to the use of DSD in refractory VF cardiac arrest. This systematic review was commissioned by the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) task force. This review was registered with PROSPERO (CRD: CRD42020152575) and is reported in accordance with the Preferred

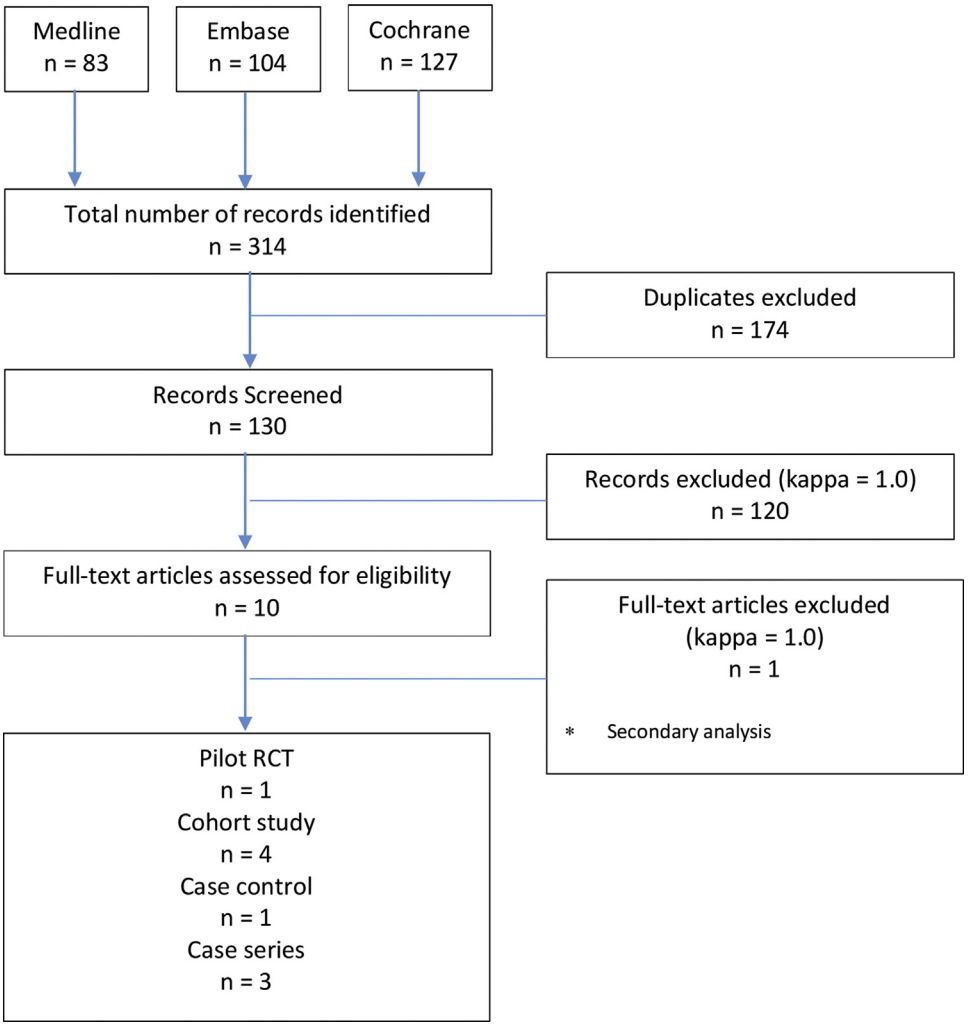

Fig. 1 – PRISMA flow diagram (final search 28 Feb 2020).

Table 1 – Characteristics of included studies.

Author	Date	Study type	Patient No.	DSD technique
Beck,	2019	Cohort	310	3 + Failed Conventional Shocks
Cabanas, J	2015	Case Series	10	5 + Failed Conventional Shocks
Cheskes, S	2019	Cohort	252	6 + Failed Conventional Shocks
Cheskes, S	2020	Pilot RCT	91	3 + Failed Conventional Shocks
Cortez	2016	Case Series	12	3 + Failed Conventional Shocks
Emmerson	2017	Cohort	220	6 + Failed Conventional Shocks
Mapp	2019	Case-control	128	3 + Failed Conventional Shocks
Merlin	2016	Case Series	7	3 + Failed Conventional Shocks
Ross	2016	Cohort	279	4 + Failed Conventional Shocks

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10]

Search strategy and selection criteria

We searched bibliographic databases (Embase, Pubmed, Cochrane) from database inception to September 27, 2019. Our search strategy, adapted for each database, used a comprehensive combination of subject headings and keywords for the three concepts of defibrillation, cardiac arrest, and patient outcomes, combined using the Boolean operator "AND". Our search was modified from the 2015 search strategy used for the 2015 ILCOR Defibrillation CoSTR.[11] We searched clinical trial registries (www.clinicaltrials.gov, www.isrctn.com, and http://www.who.int/ictrp./en/) to identify ongoing clinical research. We also hand-searched reference lists of key articles to ensure key articles had not been overlooked. No language limits were applied. Our search was repeated on February 28, 2020 to identify any additional relevant studies that were published during our review process. The search strategies can be found in Appendix A.

Our population of interest was adult patients with a shockable (VF/pVT) cardiac arrest rhythm in any setting. We were interested in comparing the use of double sequential defibrillation (DSD) to standard defibrillation strategies. We included randomized and non-randomized clinical trial designs as well as observational research studies (cohort studies, case-control studies, and cross-sectional studies). We excluded case studies, case series with less than five cases, conference abstracts, simulation studies, and protocols specifically developed for clinical trials, as well as studies for which we were unable to abstract data required to calculate our outcomes of interest.

Our pre-defined outcomes of interest were termination of VF/pVT (important), return of spontaneous circulation (important), survival to hospital admission (important), survival and/or good neurological outcome at hospital discharge, 30 days, or greater than 30 days (critical).

Two members of the research team (CD & JS) independently performed article screening at the title, abstract, and full manuscript level. Discrepancies between reviewers were first resolved through consensus, followed by a third reviewer if required. Kappa statistics were calculated for the abstract and full manuscript review. Data abstraction occurred utilizing double data abstraction. Two members of the team (CD and JS) independently abstracted data. Again,

Table 2 – Risk of bias of included studies.

Observational Studies Using Robins-I

Author	Year	Confounding	Selection	Classification of Interventions	Deviation From Intended Intervention	Missing Data	Outcomes	Selective Reporting	Overall
Mapp	2019	Serious	Moderate	Moderate	Low	Serious	Low	Low	Serious
Cheskes	2019	Critical	Moderate	Low	Moderate	Moderate	Low	Low	Critical
Beck	2019	Serious	Low	Low	Low	Low	Low	Low	Serious
Emmerson	2017	Critical	Low	Low	Moderate	Low	Low	Low	Critical
Ross	2016	Critical	Low	Low	Moderate	Moderate	Low	Low	Critical
Merlin	20016	Critical	Serious	Low	Low	Low	Low	Low	Critical
Cortez	2016	Critical	Critical	Low	Moderate	Low	Low	Low	Critical
Cabanas	2015	Critical	Serious	Low	Low	Critical	Low	Low	Critical

Randomized Controlled Trial Using ROB-2

Author	Year	Randomization	Selection	Deviation from intended intervention	Missing Outcome	Outcome Measurement	Selective Reporting	Overall
Cheskes	2020	Some concern	Some concern	Some Concern	Low	Low	Low	Some Concern

Table 3 – GRADE evidence profile table.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Double (or dual) manual defibrillation strategy	Standard manual defibrillation strategy	Relative (95% CI)	Absolute (95% CI)		
Neurologically intact survival: {Ross 2016 14}{Mapp 2019}												
2	Observational studies	Very serious[a]	Not serious	Not serious	Serious[b]	None	Ross 2016: 3/50 (6%) vs 26/229 (11.4%)		Ross 2016: 0.53 95% CI 0.17-1.68	Ross 2016: 54/1000 fewer 95% CI from 115 fewer to 54 more	⊕OOO VERY LOW	CRITICAL
							Mapp 2019: 3/25 (12.0%) vs 20/103 (19.4%)		Mapp 2019: 0.62 95% CI 0.20-1.92	Mapp 2019: 74/1000 fewer 95% CI from 191 fewer to 117 more		
Survival to hospital discharge: {Beck 2019}{Emmerson 2017}{Mapp 2019}{Ross 2016}												
4	Observational studies	Very serious[a]	Not serious	Not serious	Serious[b]	None	Beck 2019: 10/71 (14%) vs 49/239 (21%)		Beck 2019: 0.69 95% CI 0.37-1.29	Range from a low of 64/1000 fewer 95% CI from 135 fewer to 51 more (Ross 2016) to a high of 4/1000 more 95% CI from 60 fewer to 119 more (Emmerson 2017)	⊕OOO VERY LOW	CRITICAL
							Emmerson 2017: 3/45 (6%) vs 11/175 (6%)		Emmerson 2017: 1.06 95% CI 0.31-3.64			
							Mapp 2019: 4/25 (16%) vs 24/103 (23%)		Mapp 2019: 0.69 95% CI 0.26-1.80			
							Ross 2016: 4/50 (8%) vs 33/229 (14%)		Ross 2016: 0.56 95% CI 0.21-1.50			
Survival to hospital admission: {Beck 2019}{Emmerson 2017}{Mapp 2019}{Ross 2016)												
4	Observational studies	Very serious[a]	Serious	Not serious	Serious[b]	None	Beck 2019: 25/71 (35%) vs 117/239 (49%)		Beck 2019: 0.72 95% CI 0.51-1.01	Range from a low of 137/1000 fewer 95% CI from 256 fewer to 6 fewer (Beck 2019) to a high of 28/1000 more 95% CI from 89 fewer to 178 more (Emmerson 2017)	⊕OOO VERY LOW	IMPORTANT
							Emmerson 2017: 10/45 (22%) vs 34/175 (19%)		Emmerson 2017: 1.14 95% CI 0.61-2.14			
							Mapp 2019: 12/25 (48%) vs 52/103 (50%)		Mapp 2019: 0.95 95% CI 0.61-1.49			
							Ross 2016: 16/50 (32%) vs 81/229 (35%)		Ross 2016: 0.90 95% CI 0.58-1.41			
Return of spontaneous circulation: RCT {Cheskes 2020} Non-RCTs {Beck 2019}{Cheskes 2019}{Emmerson 2017}{Mapp 2019}{Ross 2016}												
1	Randomized trials	Serious[d]	Not serious	Not serious	Serious[b]	None	22/55 (40%) vs 9/36 (25%)		1.60 95% CI 0.83-3.07	150/1000 more 95% CI from 50 fewer to 323 more	⊕⊕OO LOW	IMPORTANT
5	Observational studies	Very serious[a, c]	Serious	Serious	Serious[b]	None	Beck 2019: 28/71 (39%) vs 144/239 (60%)		Beck 2019: 0.65 95% CI 0.48-0.89	Ranges from a low of 208/1000 fewer 95% CI from 355 fewer to 4 more (Mapp 2019) to a high of 29/1000 more 95% CI from 117 fewer to 190 more (Emmerson 2017)	⊕OOO VERY LOW	IMPORTANT
							Cheskes 2019: 9/51 (18%) vs 43/201 (21%)		Cheskes 2019: 0.82 95% CI 0.43-1.58			
							Emmerson 2017: 17/45 (38%) vs 61/175 (35%)		Emmerson 2017: 1.08 95% CI 0.71-1.66			
							Mapp 2019: 5/25 (20%) vs 42/103 (41%)		Mapp 2019: 0.49 95% CI 0.22-1.11			
							Ross 2016: 14/50 (28%) vs 86/229 (38%)					

(continued on next page)

Table 3 (continued)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Double (or dual) manual defibrillation strategy	Standard manual defibrillation strategy	Relative (95% CI)	Absolute (95% CI)		
									Ross 2016: 0.75 95% CI 0.46-1.20			
Termination of Ventricular Fibrillation: RCT {Cheskes 2020} Non-RCT {Cheskes 2019}												
1	Randomized trials	Serious[d]	Not serious	Not serious	Serious[b]	None	42/55 (76.4%)	24/36 (66.7%)	1.15 95% CI 0.87-1.51	97/1000 more 95% CI from 86 less to 285 more	⊕⊕OO LOW	IMPORTANT
1	Observational studies	Very serious[c]	Not serious	Not serious	Serious[e]	None	39/51 (76%)	157/201 (78%)	0.98 95% CI 0.83-1.16	16/1000 less 95% CI 158 less to 97 more	⊕OOO VERY LOW	IMPORTANT

CI, confidence interval; RR, risk ratio explanations.
[a] No risk adjustment.
[b] Large 95% CI spanning the null effect.
[c] Failure to develop and apply appropriate eligibility criteria (inclusion of control population).
[d] Significant Deviation from intended intervention.
[e] Optimal information size criterion is not met.

discrepancies were resolved through discussion to reach consensus, followed by use of a third reviewer as required. Risk of bias of individual studies was assessed using the Robins-I tool for observational studies[12] and the Cochrane Risk of Bias 2 (ROB-2) tool for clinical trials[13]. The overall certainty of evidence is reported in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guidelines.[14] All statistical analyses were performed using R version 1.2.5 (Vienna, Austria)[15] and the *meta* package.[16]

Results

The final search was performed on February 28, 2020 and spanned studies published from database inception to the date of the search. Overall, after duplicates were removed, we included a total of 130 articles for review. Hand searching of key articles and expert consensus did not identify any additional articles for inclusion. One-hundred twenty (92%) were excluded at the title and abstract review (kappa = 1.0). Another article was removed at the full manuscript review stage as it was a secondary analysis (kappa = 1.0). This resulted in 9 studies included for analysis. These included cohort studies ($n = 4$), a pilot randomized controlled trial (RCT) ($n = 1$), matched case series ($n = 1$), and multiple case series ($n = 3$). (Fig. 1) All of the studies were published in 2015 or later. The studies included a total of 1581 adult patients, 326 (20.6%) of whom had DSD applied. The characteristics of each included study are reported in Table 1.

Risk of bias for individual studies

Across the eight included observational studies, we assessed the overall risk of bias as critical in six studies, and serious in two studies. (Table 2) Critical risk of bias was mainly as a result of a critical risk of confounding due to a lack of adjusting for covariates. There was also increased risk of bias due to selection of patients in a number of studies and missing data in two studies. The risk of bias for the pilot RCT was assessed to have some concerns mainly due to 10% deviation from intended intervention (all to the standard arm). Due to the critical risk of bias in many studies, as well as clinical heterogeneity between them the decision was made not to perform a meta-analysis. This is because we would not be confident in any pooled estimated of effect size.

Clinical outcomes

A summary of the results as well as the level of certainty around the evidence for each of our outcomes of interest is presented in the GRADE evidence profile table (Table 3). For the critical outcome of good neurological survival at hospital discharge we identified very-low-certainty evidence (down-graded for risk of bias and imprecision) from five observational studies.[17–21] Ross et al. found 6.0% (3/50) good neurological outcome with the use of DSD compared to 11.4% (26/229) with standard defibrillation (unadjusted RR 0.53, 95% CI 0.17, 1.68)[21] and Mapp et al. found survival with good neurological outcome of 12.0% (3/25) with DSD compared to 19.4% (20/103) with standard defibrillation (unadjusted RR 0.62, 95% CI 0.20, 1.92)[19] (Fig. 2). The other three included studies were all case series that found 0/10 (0.0%), 2/12 (16.7%), and 3/7 (28.6%) patients survive with good neurological outcome with the use of DSD.[17,18,20]

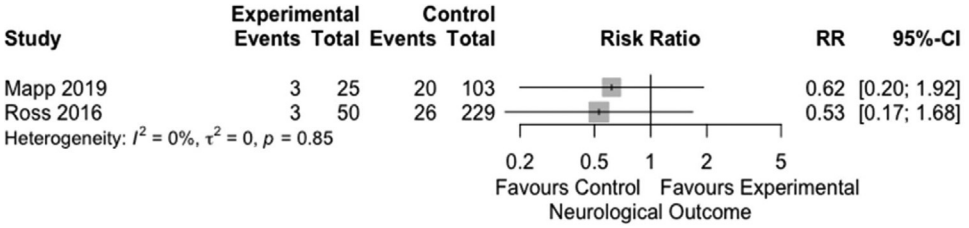

Fig. 2 – Forest plot of survival with good neurological outcome (control = standard defibrillation, experimental = DSD).

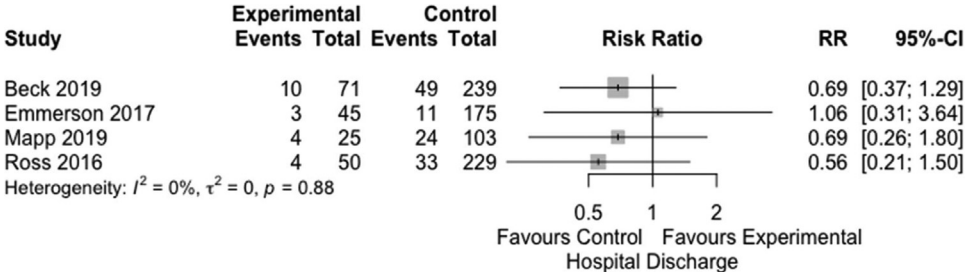

Fig. 3 – Forest plot of survival to hospital discharge (control = standard defibrillation, experimental = DSD).

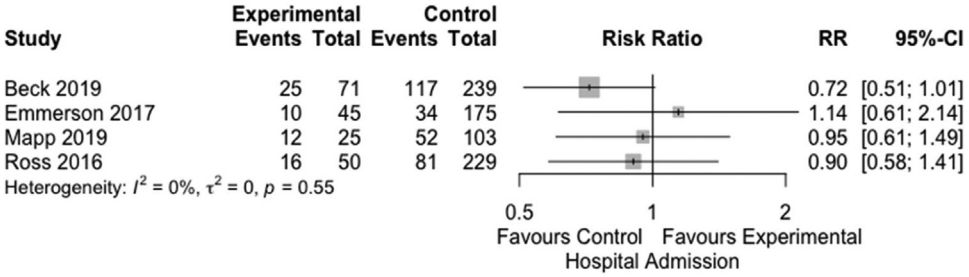

Fig. 4 – Forest plot of survival to hospital admission (control = standard defibrillation, experimental = DSD).

For the critical outcome of survival to hospital discharge we identified very-low-certainty evidence (down-graded for risk of bias and imprecision) from five observational studies with a total of 947 patients.[17,19,21–23] Ross et al. found 8.0% (4/50) survival with DSD and 14.4% (33/229) with standard defibrillation (unadjusted RR 0.56, 95% CI 0.21, 1.50). Mapp et al. found survival of 16.0% (4/25) with DSD compared to 23.3% (24/103) with standard defibrillation (unadjusted RR 0.69, 95% CI 0.26, 1.80) and Emmerson et al. found survival of 6.7% (3/45) with DSD and 6.3% (11/175) with standard defibrillation (unadjusted RR 1.06, 95% CI 0.31, 3.64). Beck et al. found survival of 14.1% (10/71) with DSD compared to 20.5% (49/239) with standard defibrillation (unadjusted RR 0.69, 95% CI 0.37, 1.29). No association was found between DSD and survival after adjusting for potential confounders (adjusted OR 0.63 95% CI 0.27, 1.45). Cabanas et al. found survival of 30.0% (3/10) in a case series of DSD cases (Fig. 3)

For the important outcome of survival to hospital admission we found very-low-certainty evidence (downgraded for risk of bias and inconsistency) from five observational studies.[19–23] Survival to hospital admission with DSD ranged from 22.2% (10/45) to 48.0% (12/45) and with standard defibrillation from 19.4% (34/175) to 50.4% (52/103) (Fig. 4). A case series reported by Merlin et al. found 57.1% (4/7) patients survived to hospital admission after the use DSD.

For the important outcome of ROSC we found low certainty of evidence (downgraded for risk of bias and imprecision) from one pilot RCT[24] and very-low-certainty evidence (downgraded for risk of bias and inconsistency) from six observational studies.[18,19,21–23,25] In the single pilot RCT, Cheskes et al. reported a ROSC rate of 40% (22/55) with DSD compared to 25% (9/36) with standard defibrillation. They also found that ROSC at emergency department arrival was 32.7% (18/55) with DSD compared to 19.4% (7/36) with standard defibrillation. (Fig. 5) In the non-randomized studies, Beck et al. found the rate of ROSC 39.4% (28/71) with DSD vs. 60.3% (144/239) with standard defibrillation. There was a significant decrease in odds of ROSC (adjusted OR 0.46, 95% CI 0.25, 0.87) with the use of DSD. Cheskes et al. found 17.6% ROSC with DSD compared to 21.4% with standard defibrillation. Emmerson et al. observed 37.8% (17/45) ROSC with DSD compared to 34.9% (61/175) with standard defibrillation and Mapp et al. observed ROSC in 20% (5/25) with DSD compared to 40.8% (42/103) with standard defibrillation. Ross et al. found 28.0% (14/50) ROSC rate with DSD compared to 37.6% (86/229) with standard defibrillation. Cortez et al. reported a case series of seven patients and found 57.1% (4/7) patients had a ROSC with DSD.

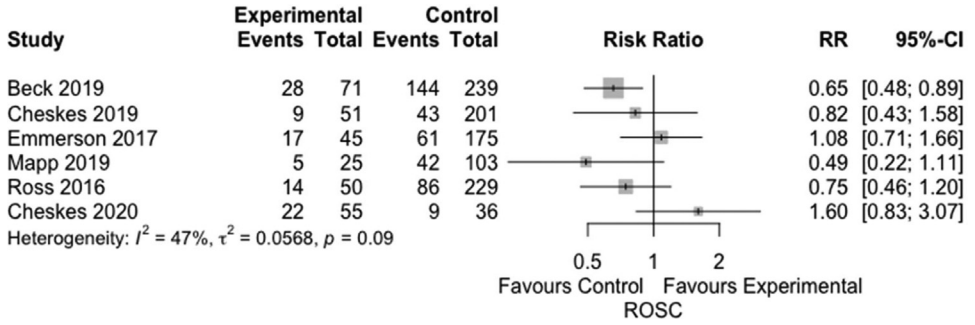

Fig. 5 – Forest plot of return of spontaneous circulation (control = standard defibrillation, experimental = DSD).

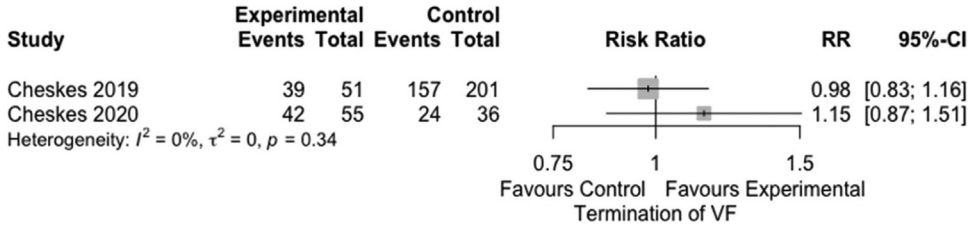

Fig. 6 – Forest plot of termination of ventricular fibrillation (control = standard defibrillation, experimental = DSD).

Finally, for our important outcome of VF termination we found low certainty of evidence (downgraded for risk of bias and imprecision) from one pilot RCT[24] and very-low-certainty evidence from four observational studies.[17,18,20,25] In the randomized study, Cheskes et al. reported VF termination with DSD of 76.4% (42/55) and 66.7% (24/36) with standard defibrillation. (Fig. 6) In a non-randomized study, Cheskes et al. reported a VF termination rate of 76.5% (39/51) with DSD vs. 78.1% (157/201) with standard defibrillation. The other three studies examining VF termination were all case series and reported rates of VF termination with DSD between 70% (7/10) and 75% (9/12).

We did not find any reports of adverse events including injury to patient, provider, or equipment damage in the included studies.

Discussion

Our systematic review found low to very-low-certainty evidence concerning the use of DSD for all outcomes. The use of DSD was associated with variable results for all the outcomes of interest. Despite additional studies published since the meta-analysis performed in 2019,[9] we too did not find any evidence to support the routine use of DSD in clinical practice. Most of the included studies had a critical risk of bias due to a lack of adjustment for potential confounders. Only one study provided adjusted data, however, we did not feel that the included covariates were sufficient to substantially reduce the risk of bias.[25] Further, three of our included nine studies were case series, which represent a significant source of selection bias.[17,18,20]

Current evidence on the use of DSD is limited by considerable clinical heterogeneity between studies which precluded a meta-analysis. We would not be confident in any estimate of effect size calculated from pooling the data provided in the included studies. Clinical heterogeneity resulted mainly from inconsistent application of DSD in clinical practice. The timing of DSD across the included observational studies varied, with most studies using DSD late in a resuscitation attempt after failure of standard resuscitation interventions. DSD was used from the third defibrillation attempt to up to 10 or more attempts. Therefore, there is a strong possibility of resuscitation time bias[26] making it difficult to draw conclusions from the included studies on the effect of DSD. There is also no reporting of ACLS interventions in most studies, which has an unknown (potentially confounding) impact on defibrillation success and termination of VF. There was also inconsistency around pad placement, energy dose delivered, and a lack of uniformity in the technique of DSD application. Finally, there is no uniform definition of what constitutes refractory VF in the included studies.

Cheskes et al. (2020) conducted the only RCT included in our review. This was an internal pilot study examining feasibility of DSD by paramedics. The study found overall high compliance to the study protocol by paramedics but was under-powered to detect differences in clinical outcomes. The study only reported short-term outcomes (ROSC and VF termination), but while overcoming the methodological limitations of observational studies, it does show different (albeit non-significant) effect estimates compared to most other studies. The results of the full RCT (clinicaltrials.gov: NCT04080986) may help to answer the question of the impact of DSD on patient survival. In addition, there are a number of knowledge gaps related to the application of DSD in cardiac arrest that remain unanswered. These include the optimal pad placement, the timing of DSD, the interval between shocks, and the optimal energy settings. Additionally, practical considerations such as the availability of two defibrillators and the documented risk of defibrillator damage[27] need to be considered in any treatment recommendation.

Conclusion

The use of double sequential defibrillation was not associated with improved outcomes from out-of-hospital cardiac arrest, however the current literature has a number of limitations to interpretation. Further high-quality evidence is needed to answer this important question.

Conflict of interest

CDD is the ILCOR domain lead for defibrillation. JS receives an honorarium from Elsevier as an Editor of Resuscitation. PM has no relevant conflicts to declare. ID is a co-author on included pilot RCT as well as an ongoing RCT related to DSD. No financial conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2020.06.008.

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