Effect of adrenaline on cardiac arrests survival

Effect of Adrenaline on Survival in Out-of-Hospital Cardiac Arrests: A Randomized Double-Blind Placebo-Controlled Trial

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The study shepherded by Jacobs et al juxtaposed the effect of adrenaline on survival in out-of-hospital cardiac arrests with a randomized double-blind placebo controlled trial. This study was the first of its kind to address the knowledge deficit of two majors goals: survival of the patient to a hospital discharge and return of spontaneous circulation (ROSC). Cardiac arrest occurring out of hospital is a significant public health issue causing fatality rates upwards of 90%, although improving in the recent decades. [1] Thus, the researchers analytically examined the relationship between the uses of adrenaline in such patients through a randomized control led trial (RCT) in the region of Western Australia (WA), under government contract with St John Ambulance Western Australia (SJA-WA).

Being on top of the studies' hierarchy, RCT studies like this one, quite evidently fortified the experiment's internal validity. The creation of comparable groups in the study allowed the control of confounding variables enhancing the internal validity. An investigation Randomi zed controlled trials , such as like RCT this one , decrease s the sampling bias by decreasing the likelihood of chance results occurring, thus enhancing the internal validity of the study . which was evident in the Jacob study. Logistic regression modeling further augmented this investigation The investigation was further augmented by logistic regression modeling which was undertaken in order to control for the effect of potential confounders [1] (i. e. the patients' initial cardiac rhythm, age and ambulance response time) . on

the relationship between study drug and patient outcome . [1] Although, as a result of a small sample size, often the case with RCTs, and specific geographical demographics, limited external validity was a given. Low external validity was evident in this study as only one major hospital in the region of WA took part in it. T he other hospitals requested did not participate due to rejection from their hospital ethics board. This was evident in this study as four of the five hospitals requested to participate felt the ethi cality of the study superseded thei r own ethical board, negatively . Hence, the total number of patients being able to participate in this study had quite drastically decreased, in turn hampering the power of the study. However, two very crucial experimental qualities in high precision and internal validity were upheld consistently throughout the experiment, in spite of the very limited external validity.

All out-of-hospital cardiac arrests attended by SJA-WA paramedics between 11 August 2006 and 30 [th] November 2009 were screened into the experiment for entry into the trial were entered into the trial. [1] . [1] Patients suffering a cardiac arrest from any cause, aged 18 years or older with resuscitation commenced by paramedics were eligible for entry as well; indicating a moderately strict eligibility and inclusion criteria. Patients were excluded based on having no resuscitation commenced, were of an age less than 18 years, and eligible patients' personal declinatio n. n and randomization number of patient lost/ As noticed, the external validity along with confounding bias of the study decreased due to the increased criterion required for a patient to take part in the trial. It may look as if few categories were used to determine the eligibility of the patient, though many factors

such as patient age, male gender, bystander witnessed, response interval, and the study drug were accounted for through univariate analysis. The only confounding variable , which was accounted for, stated by the study is the factor of initial shockable rhythm (when a particular type of cardiac rhythm is treatable using a defibrillation) – one that is not very significant (p-Value of 0. 24) in changing the efficacy of adrenaline in out-of-hospital cardiac arrests. Being able to eliminate th is ese potential confounding variable s and biases, internal validity increased showing that the lack of a causal relationship between effect of adrenaline and cardiac arrests was less likely to be an upshot of an uncontrolled confounding variable, rather than one accounted for.

In regards to a This study RCT stud y , has a sample size of 534 patients, one that is of a moderate size in comparison to other RCT studies. , out of which Out of 534 patients , 272 were randomly assigned to the group being treated with adrenaline and 262 to that of the placebo group. [1] . [1] As e E ach of the patients had a n completely equal chance to be presented with either of the treatments, and this randomization of the participants controlled for a potentiality of a sampling bias – a chance yet again enhancing the internal validity. Additionally, although very diminutive confounding bias was associated with this study, the potential of selection bias was still present as the study took place only in Western Australia. it was unable to exclude the potential for selection bias as the participation in the study by the SJA-WA paramedics was voluntary, only 40% of eligible patients were recruited. However, trial patients were well matched on baseline characteristics (age p-value of 0. 69, location of arrest p-value of 0. 25, volume of trial drug versus

placebo drug administered p-value of 0. 28) . [1] , Henceforth , no reason to suggest that paramedics who participated in the trial were more likely to selectively enroll patients into the trial. [1] . Furthermore , to reduce the possib ility of confounding bias , all paramedics in WA underwent the same type of training familiarizing them of this trial protocol ; even if they were not participating in the actual experiment. This further enhanc ed the internal validity of the study .

As mentioned above, as resuscitation commenced by paramedics, the patients were eligible for entry, where if they were administered adrenaline it would be at a rate of 1mL every 3 minutes, with no other drugs entering through tracheal administration. Prior to the commencement of each trial to be presented with an equal chance of the level of treatment for each of these patients specific training of the pharmacology of adrenaline, familiarization with the trial protocol, further practice in intravenous cannulation and cardiac simulation exercises along with testing was undertaken to ensure the prerequisite resuscitation competency standard had been achieved. This training was provided to all of the paramedics in the WA area regardless of their intention to participate in the study; being able to decline confounding bias from the patient-care givers’ aspect, enhancing the internal validity. Analyzed above in this critical appraisal are many aspects of the study that allow for a study it to be very well received by majority of the readers, although there were a couple of limitations. Firstly, the researchers were unable to achieve full patient recruitment as planned (4103 patients who had cardiac arrests attended by an ambulance). This study was designed as a multicenter trial involving a five-ambulance service

. , D d espite having ethical approval from the Human Research Ethics Committee of the University of WA, four out of five hospitals opted out. otherwise. Thus , giving this gave the study a moderate sample size, increasing the chance of making a type two error and ; essentially decreasing both the internal validity and the power of the study. The failure to achieve an adequate sample size left the trial underpowered (power of 40%) to detect significant effects on survival to hospital discharge. [1] The second limitation to the study was the ability for it to continue , as the study experimental drugs had gone past their expiry date and no additional funding was available. Grant ed, ing the patient as well as researcher blinding was well preserved in this study such that, the researchers can consider the likelihood of these factors being differentially distributed between the two study arms (placebo vs. adrenaline) to be small. [1]

The researchers claim that there is a significant (3. 4 times) increase in the likelihood of achieving ROSC pre-hospital if the patients were administered adrenaline versus the placebo (23. 5% versus 6. 4%; OR 3. 4; 95% CI 2. 0-5. 6 ; p-value <0. 00 1) . [1] They base this conclusion on the o O dds ratio (OR) , which were used to quantify the odds of achieving ROSC pre-hospital depending on the administration of the placebo or the adrenaline. how strongly the presence of the outcome was associated with the presence of the administered adrenaline versus the placebo saline solution [2] . After adjustment for confounders (age, sex, initial rhythm shockable , ambulance response interval and study drug) using the logistic regression model, there

was little change in the effect of adrenaline on ROSC (OR. 3. 5; 95% CI 2. 1-6. 0) . [1]

The degree of precision that a study maintains is defined by a confidence interval . The experimenters claim that they are 95% confident that the odds ratio of being ROSC pre-hospital with the administration of adrenaline is between 2. 1 and 6. 0 indicates a moderately definite statement (explained further) . However, there was insignificant evidence (OR 2. 2; 95% CI 0. 7 – 6. 3; p-value 0. 15) of the patient administered with adrenaline versus placebo t o surviv e until hospital discharge. Because 1. 0 is included in the confidence interval, the researchers acknowledge it as not statistically significant. However, from a clinical standpoint , 3. 5 times greater chances of the patient achieving ROSC are significant and one should definitely consider applying such a method, if in the position to do so. Results indicated the OR for ROSC achieved pre-hospital patients at 3. 4 (95% confidence interval [CI] 2. 0-5. 6; P <0. 001) indicating a significant increase in the number of patients in comparison to those tested with saline placebo. The outcomes dictate an approximate 16% greater advantage of achieving ROSC pre-hospital with the administration of adrenaline than having the placebo. Statistical significance is generally considered at 20%, but in aspects dealing with topic as such, upwards of 5% could statistically mean more to the medical community; allowing to save more lives. [3] At an OR of 2. 2 (95% confidence interval [CI] 0. 7 – 6. 3; P = 0. 15) indicates no difference between the two testing groups with the p-value greater than that of the alpha value of 0. 05. Results are further negatively supported by the CI including the value of 1, demonstrating statistical insignificance; decreasing

the study’s precision in this aspect of the outcome, although balanced by the significance in the previous outcome.

The findings of this study are equivocal to several other clinical trials designed the to assess the efficacy of adrenaline in cardiac arrest. The most dominant feature about this study is that it is the first ever-randomized placebo-controlled clinical trial of adrenaline in cardiac arrest, while others all have been non-randomized trials. Similar results were replicated through the R r esearch conducted by Olasveengen et al . a lso His study reported a doubling in the proportion of patients achieving ROSC with an OR of 1. 99 (95% confidence interval [CI] 1. 48-2. 67), and achieving similar non-significant increasing results in the proportion surviving to hospital discharge [4] . . [4] Although, Jacob’s study , although further expanded on the generality of the efficacy of drug to locations of arrests, ambulance response interval, cardiac arrest witnessed (bystander and paramedic) and airway management ; bringing greater appreciation to this study . . [1]

Three sources of Mill’s Canons were evidently utilized to support the causality. The strength of association was statistically significant, as noted by the greater effect of adrenaline in ROSC being achieved pre-hospital transportation. An increase dosage of adrenaline would directly increase ROSC, and possibly an increase number of patients survive to hospital discharge. [1, 5] Adrenaline stimulates β-adrenergic receptors which stimulate the increase of blood flow indicates the final Mill’s Canon in biological plausibility. Thus, it can be noticed that a causal relationship can be agreed upon adrenaline and increased ROSC being achieved pre-hospital.

Jacobs points out the importance of his study ’s contribution to clinical research on adrenaline usage during cardiac arrests, and at the same provides suggestions to further research avenues. To be able to determine the optimal dose or timing of adrenaline administered during cardiac arrest are the two main areas of further research. In my opinion, the study was done well done , extremely well, providing sufficient evidence for a relationship between the adrenaline and an increase ROSC in 18 and above out-of-hospital cardiac arrests. With the elimination of a majority of the biases, through the use of with logistical regression and creating comparable groups (placebo versus adrenaline) , internal validity and the precision of the study was enhanced. . The findings of this study are clinically important in that it established efficacy for the continuous use of adrenaline in cardiac arrest as currently recommended . [5] With a study related to such a topic, the sample size should adequately be increased to allow for a greater power and external validity in the study; allowing a generalization to a greater portion of the public.

References

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