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PARTIAL ORAL VERSUS INTRAVENOUS ANTIBIOTIC TREATMENT OF ENDOCARDITIS

[1]Dr. Hassan Shoaib, [2]Dr. Fatima Amin, [3]Dr. Sania Butt

[1]PGR/MO Medicine, DHQ Hospital Sheikhupura.

[2]WMO, RHC Eminabad, Gujranwala.

[3]WMO, DHQ Hospital, Sheikhupura.

Abstract:

All those patients who have ineffective endocarditis, specifically on their heart's left side are particularly given the IV antibiotics agents. A specific shift from IV to oral antibiotics to stable condition's patients once may provide better results in effectiveness and for the curative measure.

In this research, we assigned, randomly, four hundred adults, all in the steady situation who had left the side of heart endocarditis by Streptococcus, Staphylococcus aureus, coagulase-negative staphylococci and/or enterococcus feacalis and finally those who are treated through IV antibiotics. IV treatment is given to 199 patients and orally administrated patients are 201. Basic outcome of mortality, embolic events, cardiac surgery or relapse of bacteremia has been completed till six months after antibiotic treatment.

After the process of randomization, the treatment of antibiotic was accomplished after a median 19 days (from 14 to 25 days interquartile range) in the group which treated through intravenously and after 17 days, in the group which is treated by orally (P=0.48). The basic outcome happened at 12.1% rate in 24 patients with confidence interval 95% (3.4to9.6 P = 0.40).

In all those patients who suffered left side of heart endocarditis in a steady condition, a change in antibiotic treatment orally was non-inferior to sustained IV antibiotic treatment.

Keywords: *Antibiotic treatment, oral, intravenous, endocarditis, heart.*

Corresponding author:

Dr. Hassan Shoaib,

PGR/MO Medicine,

DHQ Hospital Sheikhupura.

QR code

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1.0 INTRODUCTION:

According to the American Heart Association (AHS) and the European Society of Cardiology (ESC), intravenous antibiotic agents are best for six weeks in those patients who are suffered from the left side of heart endocarditis generally. As per the starting admission phase, close monitoring and intensive care are required in most of the cases. The rate of mortality in the hospital is reported up to the 15% to 45% range as per the factors of the pathogen and in those half the patients which underwent the CVS (Cardiac-Value Surgery) (Al-Omari et al., 2014).

Most of the complicated cases shown, even death cases also, during the initial stage, accordingly, a greater patients' proportion the core reason for the hospital stay after starting phase accomplishes the treatment of intravenous antibiotic. On the contrary, if treatment of oral antibiotic may be secure and effective then a part of treatment time specifically for patients in steady conditions may take place in their homes or outside the premises of the hospital (Allen, 2006).

During long intravenous treatment and stay in the hospital may be connected with an additional complicated risk, while shorter stay has connected with healthy and better results in other disease studies. This basically shape-up regarding European and the American outpatient's guidelines; for their better treatment. Therefore, when parenteral outpatient treatment is completed then there are many logistic issues, so the staff and patient's education is highly recommended to monitor the effectiveness and severe conditions of the patients. It is found in previous researches that oral antibiotic therapy mostly minimize multiple challenges and also have may alternative opportunities (Berger, 2017).

2.0 MATERIALS AND METHODS:

2.1 Oversight and Trial Design

POET ("Partial Oral Treatment of Endocarditis) was a complete and nationwide multicentre, un-blinded and investigator-initiated trial executed in Denmark and we take that trial as our oversight and independent safety monitory design. Accordingly, that trial was certified by ethics committees of Capital Region of Denmark and similarly by the "Danish Data Protection Agency" (Berger, 2017).

2.2 Participant

All patients were 18 years of age and in a steady condition, similarly, they are receiving the treatment of intravenous antibiotic for the left side of heart endocarditis and have positive streptococcus blood cultures. Multidisciplinary team after several meeting decided about the removal of a pacemaker or to offer surgery; under the strict established guidelines and that is not a part of that trial. In this trial, only stable condition patient was enrolled (stable conditions mean that they have suitable clinical records with their initial treatment, also comprising antibiotic administrate treatment specifically intravenous for at least ten days and among those typical patients who had experienced valve surgery (Craft, 2014).

2.3 Choice of Antibiotics

IV antibiotic treatment basically managed through the guidelines of the "European Cardiology Society" with alteration which endorsed by "DSC" Danish Society of Cardiology. As shown in Table, this trial investigator established the oral antibiotic treatment with its factor of this specific trial (Iversen et al., 2018).

Component	Intravenous Treatment (N=199)	Oral Treatment (N=201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

(Source: Iversen et al., 2018)

Antibiotics, specifically which available data represented medium to high bioavailability were selected. The oral routines were founded through the calculations of pharmacokinetic and minimal inhibitory expectation concentrations regarding every bacterial species available by EUCAST ("European Committee Antimicrobial Susceptibility Testing"). Every case the testing susceptibility by disk diffusion means was established in EUCAST guidelines and accordance. Accordingly, in all cases, the oral routines may consist of two antibiotics received from multiple classes of drugs with several mechanisms of antimicrobial about the action and several processes of metabolization to mitigate the de facto monotherapy risk (Iversen et al., 2018)

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2.4 Pharmacokinetics

While confirming that all selected patients receiving enough antibiotics doses, plasma level measurement of blood samples, specifically for oral administered obtained on the first day after the single dose administration and similarly, on day five after several doses administration; with a specific assumption about steady state may be achieved by this time). Accordingly, samples were gained from those patients from IV managed group on the first day. Samples were assessed with high-pressure liquid chromatography use (Iversen et al., 2018)

For specific safety measures, the steady-state pharmacokinetics first dose was analyzed, as shown in Table below:

Applied cut-off levels for therapeutic plasma concentrations

Antibiotic	Applied cut-off levels for therapeutic plasma concentration
Rifampicin	<3 mg/L
Moxifloxacin	<2 mg/L
Linezolid	<8 mg/L
Fusidic acid	< 4 mg/L
Amoxicillin, Streptococcus spp	≤2 mg/L in <50% of the dosing interval
Amoxicillin, E. faecalis	≤8 mg/L in <50% of the dosing interval
Dicloxacillin	≤2 mg/L in <50% of the dosing interval
Clindamycin	<0.5 mg/L

(Source: Iversen et al., 2018)

2.5 Trial Procedures

Steady condition participant was swiftly assigned in the proportion of 1:1 to maintain IV administrated antibiotic treatment, with the same level of thinking to convert them to oral administrated treatment (Cunha, 2001).

2.6 Outcomes

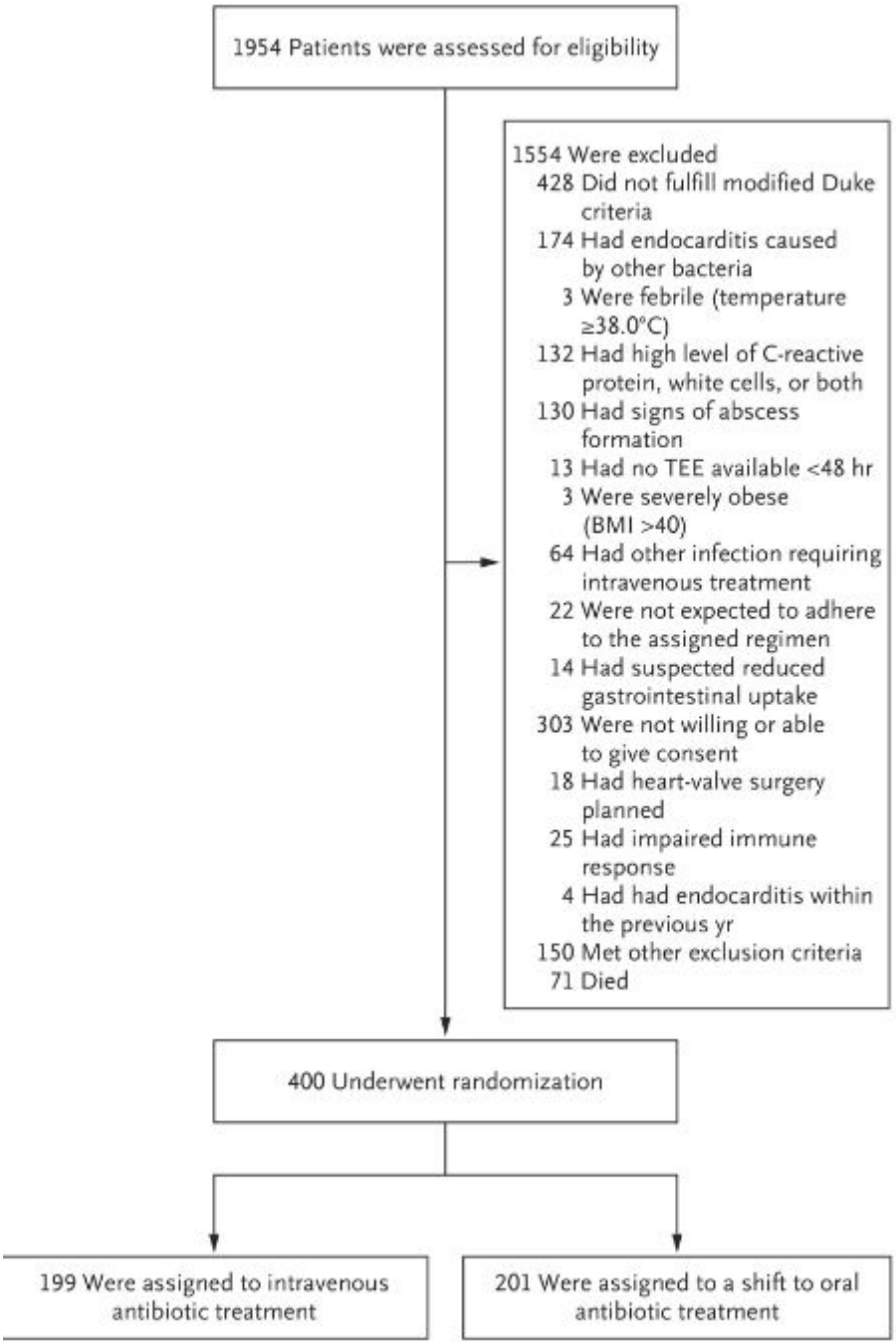
The basic outcome was basically a compound of all-cause unplanned cardiac surgery, mortality, embolic events or relapse of the basic pathogen, for specific randomization by half year follow-up from the process of randomization through half year after treatment of antibiotic. A specific clinical event committee, without known the assigned treatment plan, arbitrated the prescribed clinical results. That specific committee contained experienced cardiologists and experts in diseases of infections (Krumpe, 2013).

2.7 Statistical Analysis

This specific trial was considered as a non-inferiority trial which was specifically designed to understand the non-inferiority margin use. We further estimated the rate of events for the four factors of basic composite outcome from the review of the literature. Accordingly, we also estimated the all-cause mortality risk up to 2% to 5%, unplanned surgery risk up to 1% to 3%, embolic events risk up to 1% to 2% and relapse bacteremia risk up to 1% to 3%. So the inclusive primary outcome risk was 5% to 13%. We selected risk difference points up to 10% according to the 10% event rate assumption and follow-up loss to 5%. Similarly, we also determined the insertion about 400 patients which would be needed to provide the 90% power regarding non-inferiority confirmation with a single-sided CI of 97.5% (Krumpe, 2013).

3.0 RESULTS:

As per the duration of 6 years from 2011 to 2017 1954 patients were screened, these patients were cardiac center referred due to endocarditis suspecting for inclusion. Left side's endocarditis in 400 patients (which are 20%) of total patients) and all those fulfilled with the alteration of Duke Criteria for specific endocarditis generally enrolled (Iversen et al., 2018). From 400, 199 patients were swiftly allocated to sustained conventional IV treatment and the remaining 201 patients specifically shifted to oral treatment, as shown in Figure 1 below:



(Source: Iversen et al., 2018)

The basic reason for exclusion was 22% unverified diagnosis, the information consent inability 16% and infection 9%. Most numbers of patients were men (with the ratio of 77%) with the mean age of 67 years. Major coexisting medical condition holder patients were 35% (139 in numbers). At randomization time, the blood test results were basically identical in this group, instead of the C-reactive level of protein which was a little bit higher in IV group. Below mentioned table showing all required material about characteristics of Baseline Patients:

Characteristic	Intravenous Treatment (N = 199)	Oral Treatment (N = 201)
Mean age — yr	67.3±12.0	67.6±12.6
Female sex — no. (%)	50 (25.1)	42 (20.9)
Body temperature — °C	36.9±0.45	37.0±0.44
Coexisting condition or risk factor — no. (%)		
Diabetes	36 (18.1)	31 (15.4)
Renal failure	25 (12.6)	21 (10.4)
Dialysis	13 (6.5)	15 (7.5)
COPD	17 (8.5)	9 (4.5)
Liver disease	7 (3.5)	6 (3.0)
Cancer	14 (7.0)	18 (9.0)
Intravenous drug use	3 (1.5)	2 (1.0)
Pathogen — no. (%)†		
Streptococcus	104 (52.3)	92 (45.8)
Enterococcus faecalis	46 (23.1)	51 (25.4)
Staphylococcus aureus‡	40 (20.1)	47 (23.4)
Coagulase-negative staphylococci	10 (5.0)	13 (6.5)
Laboratory results at randomization		
Hemoglobin — mmol/liter	6.3±1.1	6.5±1.0
Leukocytes — $\times 10^{-9}$/liter	7.6±3.6	7.2±2.6
C-reactive protein — mg/liter	24.3±18.4	19.9±16.7
Creatinine — μmol/liter	124±112	141±164
Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	53 (26.6)	54 (26.9)
Pacemaker	15 (7.5)	20 (10.0)
Other known valve disease	82 (41.2)	90 (44.8)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
Mitral-valve and aortic-valve endocarditis	23 (11.6)	20 (10.0)
Endocarditis in other locations§	2 (1.0)	0
Pacemaker endocarditis	6 (3.0)	8 (4.0)
Vegetation size >9 mm	7 (3.5)	11 (5.5)
Moderate or severe valve regurgitation	19 (9.5)	23 (11.4)
Valve surgery during current disease course	75 (37.7)	77 (38.3)

(Source: Iversen et al., 2018)

According to the interquartile range from 13 to 23, the median endocarditis regarding left side time was 17 days in IV administrated group and also 17 days (according to the interquartile range 12 to 24 in oral administrated groups. Patients were further treated as per the assigned regimen, after randomization, for specific median 19 days (according to the interquartile range of 14 days to 25 days) in the group of intravenous and 17 days (according to the interquartile range of 14 to 25) in the group of orally treated. As per the data, in oral treated group 80% or 160 patients were generally or completely considered outpatients. After the randomization, the stay median length in the hospital was for 19 days (according to the interquartile range of 14 to 25 years) specifically for IV administrated group and for 3 days (with the interquartile range of 1 to 10) in the oral administrated group (P<0.001) (Iversen et al., 2018).

3.1 Antibiotic Treatment

201 patient's routines were set with the orally treated group, specifically who also had monomicrobial infections with randomization. Breakpoints and MIC also provided with the information of methicillin and penicillin in the data also. There are four patients who crossed over from the group which administrated orally to the IV administrated group (the classification of four was; one is due to nausea, one due to latest bacteremia incident specifically with

the alternative pathogen and two due to their own preferences). There is no sign of representation that any IV administrated group crossed over the oral administrated group. From randomization time, till the antibiotic therapy was accomplished 22% or 43 patients in IV administrated group was swapped to the routine of IV antibiotic, accordingly, 24 or 12% in the group treated by orally were swapped to another alternative oral regimen (P<0.01) (Krumpe, 2013).

3.2 Primary Outcome

All registered patients were straggled for six months after the treatment of antibiotic completion or till any of them may not die. There was no patient who may lose the follow-up and the basic outcome composite happened in 10.5% out of 42 patients (further classification is that 12.1% or 24 numbers of patients in intravenous administrated group and 9.0% or 18 numbers of patients in oral treated group with odds ratio of 0.72 and CI of 95%, 0.37 to 1.36. the difference between the group was 3.1% (with CI 95%, 3.4 to 9.6 P=0.40) in the support of the oral administrated group, and the non-inferiority criterion also was therefore established. In the analysis of per-protocol, the basic composite outcome happened in 12.1% or 24 from 199 numbers of patients in the IV administrated group and 9.1% from 18 from 197 oral administrated groups (the difference between groups, 3.0% with CI 95%, 3.2 to 9.2) (Krumpe, 2013).

4.0 DISCUSSION:

In all those patients who suffered from endocarditis, specifically on heart's left side generally caused by Streptococcus, aureus, E.faecalis, or coagulase-negative staphylococci which basically in steady condition and who had enough initial treatment response, through a shift from basic oral antibiotic treatment for initial IV administration to constant IV antibiotic treatment. All oral administrated group patients were swapped from IV group of treatment to oral group on about a specific day 17, which is the mid-point of the period of treatment. However, in the time period of half of the treatment the oral administrated group patients were suitable for fractional or complete case treatment (Al-Omari et al., 2014).

According to the pre-specified subgroups, the results observed constant, especially including the subgroups which described as per the valve affected type (either native valve or prosthetic valve) and as per the treatment type (such as surgery in the time period of the disease treatment). It may also need to note that basic result observed similar across different four types of bacteria. Therefore, this trial was not fuelled to confirm the basic result in pre-specific subgroup form. Primary outcome's high rate in specific patients with coagulase-negative staphylococci potentially imitates the delays in diagnosis mutual with fact that more frail patients may suffer more due to this and those who had adverse co-existing situations (Berger, 2017).

5.0 CONCLUSION:

As the concluding note, patients who had suffered from the left side of heart endocarditis instigated by Streptococcus, S. aureus, E. facials, and coagulase-negative staphylococci even with their steady condition, a swap from IV treatment group to oral antibiotic treatment group was non-inferior to the sustained treatment of IV antibiotic.

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