Abstract

Purpose: The purpose of this study was to compare clinical trials’ methodological quality between developing and developed countries, and its correlation with human development index.

Data Sources: We systematically searched the PUBMED electronic database for published controlled clinical trials conducted in heart failure. Results were filtered using the “clinical trials” filter and dated from January 2009 to December 2013.

Study Selection: From the 416 articles, 61 articles that met the selection criteria were selected. Each article was screened independently for inclusion by two independent raters.

Data extraction: Out of the 61 included articles, 53 were from developed countries and only 8 were from developing countries. Each article was assessed for their quality by five independent raters using the JADAD quality scale.

Results: Median quality score for developed countries was 3 (range 0-5), while for developing countries was 1.5 (range 0-4) (p-value 0.04). There is a statistically significant correlation between quality scores and the human development index (HDI) (rho= 0.275, p-value = 0.032). The only significant correlation between HDI indices and quality score was for education index (rho = 0.381, p-value = 0.003).

Conclusions and Relevance: Our study indicated that there is a difference between the developing and the developed countries in terms of quantity and quality of clinical trials, mainly due to differences in the educational status. Based on that, we recommend to incorporate research in the curricula of the undergraduate medical education in developing countries and to initiate collaborative clinical research courses.

Key-Words: Clinical trial quality, developing countries, developed countries, JADAD scale, human development index, heart failure.

Introduction

Randomized Clinical Trials (RCTs) and systematic reviews are considered the gold standard of judging for treatment effects due to the controlled conditions and the ease of attributing clinical outcomes to interventions (Barton, 2000). Hence, the assessment of the methodological quality of Controlled Clinical Trials (CCTs) and the identification of the most scientifically sound trials is crucial for the determination of evidence-based results in clinical practice (Jadad et al., 1996).

There are a number of ways to assess the methodological quality of clinical trials such as checklists and scales, e.g. PEDro, Delphi list, Bizzini, Chalmers, Andrew and JADAD scales. JADAD scale has been proven to have the best validity and reliability (Olivo et al., 2008).
It is a three-item, five-point scale that is known to be easy. It includes elements that have been shown to correlate with bias and has known reliability and external validity (Jadad et al., 1996).

It was previously mentioned that one third of the trials are being conducted in developing countries which raises concerns about both the ethical and the scientific features of those trials. It is believed that there are vast differences between developing and developed countries in terms of health care system, clinical research training, educational systems, socioeconomic statuses and health infrastructure. All of these factors can adversely affect the quality of trials which are being conducted in developing countries in comparison to those conducted in the developed ones (Azeka, Fregni, & Auler Junior, 2011; Hróbjartsson, Boutron, Turner, Altman, & Moher, 2013).

Therefore, our primary aim is to compare quality of clinical trials between developing and developed countries using the JADAD scale and the correlation between clinical trial quality and Human development index (HDI). Our secondary aim is to assess the relation between journal's impact factor and clinical trials' quality.

Methodology

Search Criteria

We systematically searched the PUBMED electronic database for published controlled clinical trials conducted in heart failure. We selected heart failure topic because it is a prevalent health problem among both the developing and the developed countries and thus a sufficient number of clinical trials are being conducted in it. The following MESH search terms were used: “digoxin”, “beta blockers”, “calcium channel blocker”, “diuretics”, “vasodilators” and each one of them was combined with the MESH search term “heart failure”. Results were filtered using the “clinical trials” filter and dated from January 2009 to December 2013.

Inclusion and Exclusion Criteria

We applied certain inclusion and exclusion criteria on the extracted articles. Eligible articles included controlled trials conducted in heart failure patients, with an available link to its full article and in English Language. Exclusion criteria were 1) Single arm trials, 2) Other types of studies (observational studies, reviews, meta-analyses and prognostic/ diagnostic/ biomarker studies), 3) Letters to editors, 4) Multinational trials, 5) Animal studies, 6) Pharmacokinetic studies, 7) Pilot studies, 8) Post-hoc analyses and secondary analyses of original trials, 9) Studies involving educational/ exercise/diet or surgical interventions, 10) Clinical trials which had quality of life as the only outcome and those with outcomes which are not related to heart failure and 11) Clinical trials’ protocols. Articles were screened independently for inclusion by two independent raters for each keyword/search term and then the results were matched.

Included studies were independently assessed for their quality by five independent raters using the JADAD scale. Intraclass correlation was used to assess the interrater reliability. JADAD scale is a 3-item instrument which combines information on randomization, blinding as well as description of withdrawal and dropouts in a single numerical value. To increase the reliability of the results, medians of the final JADAD scores were taken. Raters are clinical research associates with extensive skills in data collection and management, statistical analysis and clinical trials.

United Nations Development Programme data were used to identify the development parameters of the countries. HDI was used to determine the country’s development status. Average indices were calculated for the period between 2009 and 2013. Data were extracted from the United Nations Development Programme database (United Nations, n.d.). We extracted the 5 year impact factors of journals where the included articles were published from Thomson Reuters Journal Citation Reports® 2014.

Data Analysis

Median and range were used to describe scores of JADAD scale in developed and developing countries and impact factors for journals where the screened papers were published. Mann-Whitney U (Wilcoxon Rank Sum test) was used to compare scores given to developed countries versus developing countries and impact factors of papers from developed countries versus developing countries. Intraclass correlation was tested using Shrout and Fleiss method, based on fixed sets of judges for each paper (Shrout & Fleiss, 1979). The correlation between different indices used in HDI calculation, 5 year impact factor and JADAD scores were assessed using Spearman correlation coefficient. P-value cut-off was adjusted using Bonferroni correction to adjust for the increase of alpha error arising from multiple testing when testing the relation between different indices used in HDI calculation and quality scores. Statistical analysis was performed using RStudioVersion 0.98,953 (RStudio, 2014).

<table>
<thead>
<tr>
<th>Table 1. Number of articles retrieved and included for each MESH term.</th>
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<tbody>
<tr>
<td>Search Keyword</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Beta blocker</td>
</tr>
<tr>
<td>Vasodilators</td>
</tr>
</tbody>
</table>

It was previously mentioned that one third of the trials are being conducted in developing countries which raises concerns about both the ethical and the scientific features of those trials. It is believed that there are vast differences between developing and developed countries in terms of health care system, clinical research training, educational systems, socioeconomic statuses and health infrastructure. All of these factors can adversely affect the quality of trials which are being conducted in developing countries in comparison to those conducted in the developed ones (Azeka, Fregni, & Auler Junior, 2011; Hróbjartsson, Boutron, Turner, Altman, & Moher, 2013).

Therefore, our primary aim is to compare quality of clinical trials between developing and developed countries using the JADAD scale and the correlation between clinical trial quality and Human development index (HDI). Our secondary aim is to assess the relation between journal’s impact factor and clinical trials’ quality.
Results

Four hundred and sixteen articles were identified in the preliminary search using the MESH terms and filters stated in the methods section. Table 1 displays the number of retrieved articles for each MESH term. Duplicate articles (53) were excluded. Three hundred and two articles were excluded after applying the exclusion criteria and 61 articles were included in the analyses. Figure 1 shows the fate of the 416 identified articles. Table 1 shows the PMID of the excluded articles with reasons of exclusion. Intraclass correlation between different raters was 0.72 95% CI (0.63 – 0.8).

Quality Score Assessment

Out of the 61 clinical trials, 53 were from developed countries and only eight were from developing countries. Supplementary table 2 shows the PMID of the all included clinical trials, the country of origin of each clinical trial, the quality score of each rater, the median quality score with the journal names and their impact factors. Median quality score for developed countries was 3 (range 0–5), while for developing countries was 1.5 (range 0–4). The difference in ranks of quality scores was statistically significant, Mann Whitney p-value equal 0.04. Table 2 summarizes the median quality score of developed and developing countries.

Correlation between quality scores and the HDI was found to have a statistically significant weak positive correlation (rho = 0.275, p-value=0.032). When assessing the correlation between quality scores and the component indices of HDI, p-value cut-off to determine significance was adjusted to correct for multiple testing using Bonferroni correction 0.05/3 = 0.017. The only component with high statistically significant correlation was the education index (rho =0.381, p-value = 0.003), denoting that the relation can be described as moderate positive relationship. The correlation between quality of clinical trials and GNI, HI were as follows (rho= 0.277, p-value=0.031) and (rho= -0.11, p-value= 0.415). Figure 2 displays the correlation between HDI and its different indices with the median quality score.

Impact Factor Effect Assessment

Articles from developed countries were found to be published in journals that had higher median impact factor (median = 3.5) than those from developing countries (1.78). This difference was found to be highly significant, Mann Whitney p-value equal 0.001. Table 2 summarizes the median impact factor scores between developed and developing countries. The relation between impact factor and quality scores was a moderate positive relation with high statistical significance (rho= 0.4, p-value= 0.002).

Discussion

Quality evaluation facilitates the inclusion of only the studies with high quality in meta-analyses and systematic reviews. The Cochrane Review Group has recommended to assess the randomization, blinding and attrition of any trial before its inclusion in a meta-analysis (Hróbjartsson et al., 2013). In addition to that, assessing the methodological quality could explain the heterogeneous and discordant results among studies with the same research question as trials with different qualities could have different conclusions(Jadad et al., 1996)(Juni, 2001). For example, Moher and colleagues found that trials that did not report aspects such as blinding and allocation concealment tended to give more exaggerated treatment effects compared to those which reported those aspects(Olivo et al., 2008).

Throughout our study, we identified 53 heart failure controlled clinical trials conducted in developed countries compared to only 8 conducted in developing countries. The deficit in the quantity of clinical trials in developing countries is a probable reason for the significant difference in quality scores between developed and developing countries.
countries is not surprising as it has been supported in previous studies. Broeck and Robinson have indicated that drug research is limited in the developing world due to the limiting resources (Van den Broeck & Robinson, 2007). The practical use of science and technology and the investment of industry in research have created the environment where there is an increased emphasis on research in the developed world (Keyworth, 1984). In an article by Nobel-winning As Abdus Salam, the author mentioned that developing countries view science as a "marginal activity" and although this article dates back to 1987, this fact has not changed much in various developing states. Education, research and technology are the main instruments for accelerating development and therefore it is no wonder that the countries' developmental status are relevant to their education index (Salam A, 1978).

A clinical trial having a total JADAD score of more than or equal to 3 is considered to be of a high quality, while that has a total JADAD score of less than or equal to 2 is considered to be of a low quality (Jo et al., 2013). In our study, there was a statistically significant difference in the JADAD quality scores between the developing countries (median score 1.5) and the developed countries (median score 3) (Mann Whitney p-value= 0.04). Thus, our results indicate that the clinical trials which were conducted in the developed countries are of high quality while those that were conducted in the developing countries are of low quality. These results only prove the hypothesized difference in quality depicted in numbers.

HDI is used to classify countries into developing and developed countries. Countries below 0.8 are classified as developing countries. HDI is a composite scale measuring health, education and economical state of countries. Health index (HI) is measured using life expectancy at birth. Education (EDU) is measured by mean of years of schooling for adults aged 25 years and expected years of schooling for children of school entering age. Economical state is measured by gross national income per capita (GNI).

There was a significant correlation (rho= 0.275, p-value= 0.032) between the JADAD quality scores and the human development index (HDI). The HDI is a reflection of the nation's education, quality of life and income. We further analyzed the correlation between the JADAD scores and each one of the main components of the HDI (education index, the country gross national income per capita and the health index).

Table 2. Quality score and 5 year impact factor between developed and developing countries

<table>
<thead>
<tr>
<th>Quality Score</th>
<th>N</th>
<th>Median (Range)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed</td>
<td>61</td>
<td>3.00 (0-5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Developing</td>
<td>52</td>
<td>3.50 (1.07-29.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>3.46 (1.07-29.91)</td>
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</table>

* Mann-Whitney U test

After applying the Bonferroni correction for multiple tests, the only statistically significant correlation was found between the education index and quality scores (r= 0.381, p-value 0.003). This could be attributed to the prioritization of education and its influence on research culture in developed countries. Lang and Siribaddana have stated that there is an under-representation of the developing countries in clinical research, mainly due to lack of knowledge, training and experience of the researchers there (Lang & Siribaddana, 2012). Also, as highlighted in Deckelbaum et al article, teaching, infrastructure and even motivation to study the basic science are clearly deficient in the developing countries (Deckelbaum, Ntambi, & Wolgemuth, 2011). In addition to that, governments in the developing countries are demotivated to incorporate research in the undergraduate education which has been proven to have great positive effects through improving the students’ critical thinking skills and through the application of science in real projects (Alamodi et al., 2014).

GNI reflects the economic situation of the country, as it is based on purchasing power parity. There was no statistically significant correlation between standard of living index and quality scores (rho= 0.277, p-value=0.031). These results indicate that standard of living index may have a weak relationship with the quality of clinical trials. For instance, countries like Qatar and Kuwait are considered from the highest GNI (rank 1 and 3 respectively), but we weren’t able to find any clinical trial matching our search criteria.

Our study revealed a statistically significant positive relationship between the clinical trial quality and the journal’s five year impact factor (p-value= 0.002). The conclusion that clinical trials with higher quality are published in journals with a higher impact factor was supported in previous studies. Gluud et. al indicated that
Also, Kuroki et al. concluded that statistical association between the quality of published CTs, whereas private nonprofit funding was associated with the highest quality scores in comparison to others sponsored by industry (Rochler, 1991; Lee et al., 2011). The International Council for Science (ICSU) reported that newly industrialized countries “North America, Europe, Japan, and Asian” are responsible for 85% of world expenditure in science and technology even though they represent less than 25% of world’s population in contrast to only 0.5% is the share of sub-Saharan Africa (Deckelbaum et al., 2011).

Although the previously mentioned factors play a major role in the quality of research papers, few studies express contrary results; a negative correlation between the quality scores and journal impact factor, source of funding and the quality of research studies. On the other hand; reported methodologies, data integrity, randomization, allocation methods and trial designs are in real need for improvement. Therefore, more education and training in developing countries is required to upgrade the quality of research (Bhatt, 2011; Clark et al., 1999; Holngren & Schnitzer, 2004; Jo et al., 2013). A major strength in our study was the use of the JADAD quality scale which is an easy, short and simple tool for assessing the clinical trial quality. It takes into account the most important trial aspects (randomization, double blinding and explanation of dropouts) which can greatly affect its quality and can result in bias if they were not appropriately implemented. Also, it has been evident that the JADAD scale has the best validity and reliability among the other used quality scales (Olivo et al., 2008). Although this scale was developed mainly to assess the methodological quality of the pain clinical trials, it might be applied to other different area of medicine as none of its items is specific to pain research area (Bhatt, 2011).

We identified a number of limitations in our study. Some of them are related to the JADAD scale. Unfortunately, JADAD scale does not address several other points that may affect the quality of clinical trials such as clinical relevance of the research question, statistical analysis, a priori sample size calculation, ethical issues, the inclusion/ exclusion criteria and outcomes (Olivo et al., 2008). It is also associated with low inter rater agreement which was overcome by using the median of the 5 independent reviewers (Clark et al., 1999). JADAD scale can wrongly assume that a certain trial has a low quality despite being appropriately designed, conducted and analyzed due to the fact that its reporting is deficient (Huwyler-Müntener, 2002; Jadad et al., 1996; Olivo et al., 2008). In addition to that, the HDI which was used to classify the countries as developed and developing does not reflect on inequalities, poverty, human security, empowerment, etc (Hou, Walsh, & Zhang, 2014; Noorbakhsh, 1998; Sagar & Najam, 1998). Our small sample size especially from the developing countries and the fact that we only searched the Pubmed database can
adversely affect the validity of our results. Although, we tried to overcome this by using a topic such as “heart failure” which is prevalent in both developing and developed countries. One final limitation was that we were not able to blind the evaluators to the nationalities of publications. However, the bias arising from such a problem may have been greatly reduced by using the median of 5 independent raters, given that the intraclass correlation between the raters (0.72) can be considered good.

In conclusion, our study indicated that there is a difference between the developing and the developed countries in terms of quantity and quality of clinical trials. To our knowledge, this is the first study to be conducted with that objective. Therefore, we encourage further investigation of this issue in the future using larger sample sizes, different topics and different quality scales. Based on the results of this study, we recommend to incorporate research in the curricula of the undergraduate medical education in developing countries. The experience ofalfaisal University in the Saudi Arabia in incorporating research in undergraduate education had outstanding outcomes as 50% of the undergraduate students had published their articles in peer-reviewed journals (Alamodi et al., 2014). Another approach is initiating collaborative courses between developing and developed countries. One significant example of those initiatives is the 'Principles and Practice of Clinical Research' course by Harvard Medical School. Also, one of the effective ways to solve this problem is to encourage governments in the developing countries to increase the creativity and critical thinking abilities of the students through developing new educational tools. This can be achieved by convincing the policy makers in those countries with the importance of clinical research, not only for healthcare improvement, but also for economic enhancement through increasing the human productivity (Deckelbaum et al., 2011).

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Conflict of interest and financial disclosure
The authors followed the International Committee of Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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