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Original Article

Reporting of Ethical Considerations Associated with Clinical Trials Published in Iranian Dental Journals between 2001 and 2011

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Abstract

Background: Ethical consideration is a basic requirement for design of randomized clinical trials. The purpose of this study was to assess whether reports of Iranian dental clinical trials complied with the requirements of the ethical principles of human research.

Methods: In this retrospective observational study electronic search was performed to identify all dental clinical trials published between 2001 and 2011. Each trial report was assessed for inclusion of a statement that 17 items about research ethics.

Results: Totally 242 papers were identified, of which 15.3%, stated that ethical approval had been obtained and 50.4% of the trial reports indicated that informed consent had been obtained. The mean ethical score for the mentioned studies was 7/68 out of 17.

Conclusions: Most Iranian dental clinical trial reports failed to consider important ethical principles. The reporting of the ethical issues associated with these trials could be improved further not only by the instructions to authors, but also by Journal editors refusing to publish trials that do not comply.

Keywords: Ethics, Clinical Trials, Journal, Dental, Iran

Introduction

Every research is inevitably associated with ethical considerations and with advances in science, observance of ethical guidelines becomes ever-increasingly important (1,2). A wide range of medical ethics theories have been applied to human research studies (3). Use of human subjects in medical research has a long history; however, since late 1960s serious attention has been focused on ethical issues in such studies (4). Scientific and ethical standards in relation to biomedical research on human subjects are rooted in international protocols, which have been designed according to accurate evaluations of human ethical needs to facilitate and support ethical considerations worldwide (5). Some of the most famous ethical protocols include the International Nuremberg Code, Helsinki Declaration, Belmont Report and ICP and GCP (Good Clinical Practice) (6-8). Strict observance of these protocols helps preserve dignity, rights and health of the participants in human research studies.

Several ethical issues have been implicated in the ethical aspects of interventional research studies. RCTs (Randomized Clinical Trials) are the gold standard of such research studies and are generally the best method to evaluate the effect of a new medication or a new treatment modality (9–11). Based on what was discussed above, it appears necessary to minimize injuries inflicted on subjects and patients during RCTs (12). Various new

therapeutic techniques are widely introduced and used in dentistry and RCTs are required to confirm these treatment modalities (13). Human rights and ethical considerations in research studies in the field of oral health are consistent with other human studies and the principles are based on international agreements; some of these principles include respect for the dignity of all the humans, respect for the principle of participation by one's own volition, respect for the confidentiality of personal information, attempt to reduce damages and injuries and increase benefits as far as possible and the scientific authenticity of the study (14). The most important ethical codes in clinical trials include the necessity to gain approval of the protocol from the ethics committee (15) and to obtain informed consent from the subjects (16,17), participation by free will of the subjects, infliction of no extra costs on or wasting of the time of the subjects, confidentiality of personal information, absence of any risks for the subjects, allowance for compensation of any inadvertent damages and injuries to the participants during the study, permission to voluntarily drop out of the study, no use of only available populations for the purpose of the study, infliction of no pain and stress on the patients during their routine daily lives (18).

RCTs have expanded significantly in dentistry in many developing countries in recent years. It is obvious that these trials should be designed according to ethical principles so that the rights and health of the subjects can be guaranteed. However, based on reports available strict observance of ethical principles in RCTs in developing countries, including countries in the Middle East, has been neglected (19). It is necessary for patients and clinicians to ethically interpret the results of studies to make sure about the validity of new knowledge acquired and lack of commitment to ethical principles might lead to unpleasant consequences for patients (including overestimation of benefits and underestimation of damages and injuries); this incorrect administration of research studies is a serious threat to the general health of human beings (20).

The present study was undertaken to evaluate observance of ethical principles in RCTs published in Iranian dental journals during the recent decade.

Methods

In this cross-sectional study, all the RCTs in the field of dentistry, which had been published in Iranian scientific/research journals from the beginning of 2001 to the end of 2010 and indexed in valid databases such as Scopus, CINAHL and Embase, were collected. To this end, the website of the Iranian Ministry of Health, Treatment and Medical Education at www.bhi.ir and also the website, www.sid.ir, were referred to and a list of journals approved by the Medical Journals Committee of the country, with scientific/research status, were provided; subsequently, dental journals were determined on the list. The websites of all these journals were referred to and full texts of all the RCTs published during the period in question were saved. The key words "trial" and "clinical trial" combined with "dentistry" were used to retrieve RCTs. Data is relation to the journal title, year of publication and the specialty field of the relevant article were collected and recorded. The full texts of all the articles were separately read by two reviewers and a checklist was completed for each article. The checklists were reviewed and the cases for each article, which the two reviewers had not agreed upon, were determined and were discussed in a joint session and a final agreement was reached. The checklist prepared by the researchers was used as a tool to evaluate the ethical issues of the RCTs collected. The checklist consisted of 17 questions designed by referring to valid sources (international and Iranian ethical guidelines and codes) so that all the ethical aspects of RCTs could be evaluated. To this end, two valid ethical checklists approved by universities of Bristol and Boston were reviewed. These two checklists are based on international ethical protocols (21, 22). A point of "1" or "0" was assigned to each ethical code in the checklist, which corresponded to two situations of "observance" and "no observance",

respectively. The 17 questions on the questionnaire were divided into two aspects with positive ethical connotations (items 1–9) and negative ethical connotations (items 10–17).

The value of ethical considerations of an RCT increased with an increase in the positive aspects and a decrease in negative aspects. The response to questions with negative connotations were entered in a computer (SPSS 17) by taking into account the "reverse coding" and the reverse form was used for calculation of the scores of articles and for analysis, i.e. if the case existed in the study (a positive response) a score of "0" and in its absence (a negative response) a score of "1" was assigned to that questions. Therefore, the total score of ethical considerations for each article was obtained by summing up the scores of all the questions, which was a score between "0" and "17". The total score approached 17 in RCTs with a higher level of observance of ethical considerations (more positive responses to questions 0–9 and more negative responses to questions 10–17); conversely, the total score approached "0" in RCTs with low level of observance of ethical considerations (more negative responses to questions 0–6 and more positive responses to questions 10–17). Frequency statistics were used to calculate the observance level of ethical guidelines; independent t-test and linear regression were used to compare the variables in question.

Results

In the present study, full texts of 242 articles were collected after running a search for RCTs at the time interval in question. A total of 194 articles (80.16%) were in Farsi and 48 articles (19.84%) were in English. The articles were placed in 10 specialty fields. The most numerous articles were in periodontics, pediatric dentistry and oral medicine (36.36%, 16.11% and 14.87%, respectively), with the least numerous ones in oral pathology and radiology (0.41% and 0.82%, respectively).

Figure 1 presents the frequency percentages of 17 items. As the figure shows the most observed positive item was item No. 2 (obtaining a consent form) in 50.4% of the articles. The two items of 6 and 7 (safety of the tests for the subjects and presence of an ethical code) ranked second and third with observance rates of 34.7% and 15.3%, respectively. The figure shows that items 3, 4 and 4 (infliction of no extra costs and time on the subjects, presenting gifts to the subjects, and confidentiality of the personal information of the subjects) had not be observed in almost any of the studies evaluated, with observance rates of 0.8%, 0% and 0.4%, respectively. In addition, items 1, 8 and 9 (participation by volunteering, compensation of possible damages and injuries, and permission to drop out by volition, respectively) had been observed in only 10.3%, 6.6% and 4.5% of the studies evaluated, respectively.

The most common item with a negative connotation was item 10 (use of the population available) (64.4%); items 12, 15 and 14 (induction of pain and discomfort, repetitive and long measurements, and the need for the consent of a guardian to take part in the study, respectively) ranked second to fourth with 42.1%, 39.6% and 4.9%, respectively. None of the studies evaluated had items 11, 13 and 16 (participation in sensitive discussions, induction of stress in daily routines of life, and use of dubious sources, respectively).

The ethical issue of administration of a placebo (item 17) had been observed in only 4.1% of the articles. The final mean score of the articles evaluated in the present survey was 7.68 of the maximum score of 17. The highest scores belonged to articles on pathology [9] , radiology [8.5] and orthodontics [8.1] ; in contrast, the least scores were assigned to articles on surgery, periodontology and endodontics, with all the scores less than 7.6. Linear regression showed no significant relationship between the overall mean scores of the articles and the publication year, and the specialty field of the articles and the language of the articles ($P>0.05$), i.e., regression analysis showed that from 2001 on, differences in the fields of the articles (including oral medicine, pediatric dentistry etc) or the English or Farsi languages of the RCT articles in Iran has not had any effect on the observance of ethical principles in such studies.

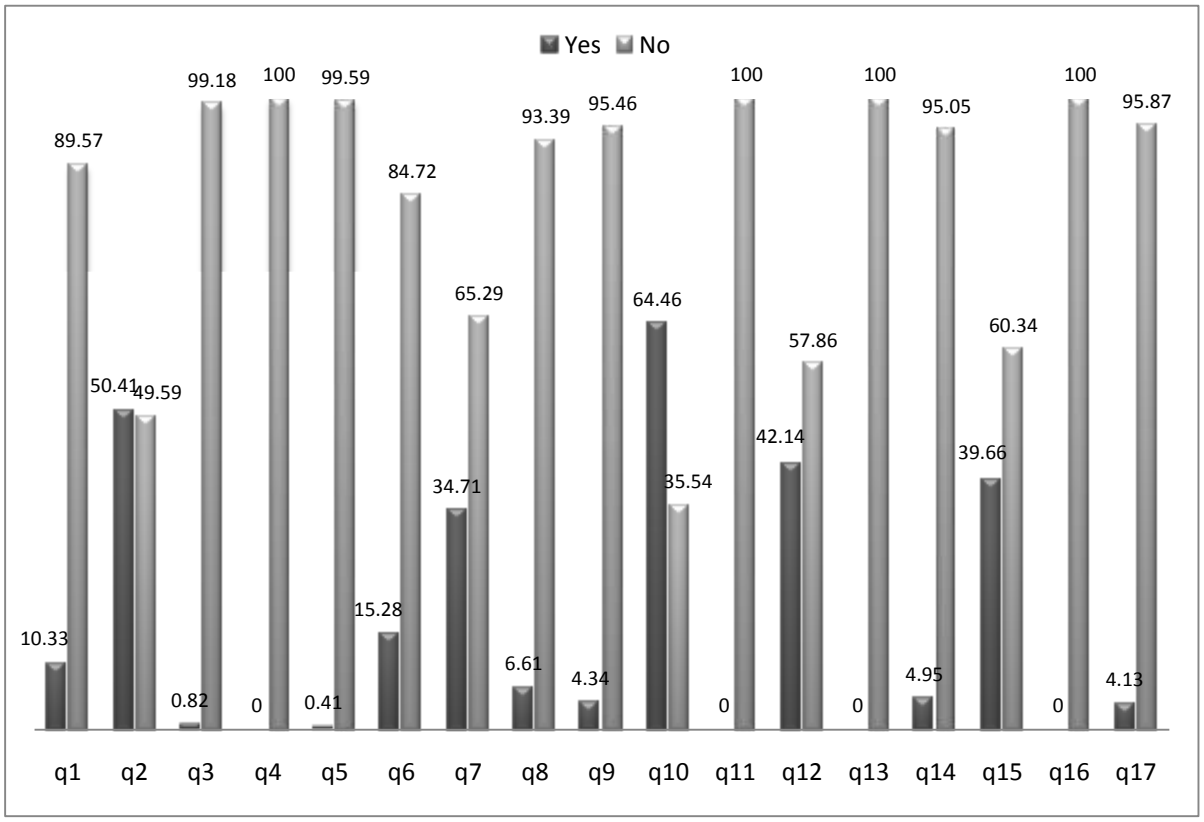

Fig. 1: Frequency of 17 Ethical Items observed in 242 Articles

q1- Have the subjects participated in the study voluntarily?
q2-Have the participants completed and signed consent forms?
q3-Has the study protocol imposed any extra costs on or has it wasted the time of the participants?
q4-Have the participants received any gifts, free medicines or …… for their participation?
q5-Has the personal information of the participants and the results been kept confidential through out the study?
q6-Does the study have any ethical codes?
q7-Have the tests been safe for the subjects?
q8-Has compensation of any possibly inadvertent injuries to the subjects been considered?
q9-Have the participants been free to drop out of the study at their own volition?
q10-Have only available populations been included in the study, i.e. mentally retarded subjects, prisoners, patients referring to treatment centers or the health care system professional personnel?
q11-Has the study implicated itself in discussions of sensitive issues?
q12-Has the study resulted in pain or discomfort (even minor) in the subjects?
q13-Has the study led to the induction of stress in the daily lives of participants?
q14-Has the participation of the subjects in the study involved gaining permission from a guardian?
q15-Has the protocol of the study necessitated long and repetitive measurements?
q16-Have invalid and dubious sources have been used to carry out the study?
q17-Was it ethically acceptable to administer a placebo?

Discussion

Ethical guidelines and principles are not always without any changes and both can undergo changes under certain conditions, i.e. observance of ethical issues of any human research cannot respond to all the ethical aspects in question all over the world (2). In the present study, in 84.7% of RCTs evaluated the approval of research ethics committees for the implementation of the study had not been mentioned. However, in some countries in the Middle East, 28% of researchers had not obtained the approval of ethics committees for their research (19). Dal-Re et al. (23) Reported that obtaining the approval of an ethics committee is to some extent time-consuming and on the average, there is a time interval of 20 days between the decision making of a committee and notifying the researchers. In addition, it appears the attitude and commitment of the members of such committees and the knowledge, skill and experience they have gained in ethical evaluation of RCTs are important factors affecting the efficacy of their performance (23). It should be pointed out that the rate of ethical approval obtained in the present study was higher than that in a study by Harrison (16.1%) (24). Medical sciences universities and research centers, as the bodies responsible for such research studies in our country, should pay more attention to the selection of members and performance of such committees. In some countries, such as Canada, the majority of RCTs have been shifted from academic institutions to hospitals during the past decade, which has resulted in multiplicity of ethics committees and as a result, in problems after disagreements between the members of such committees in relation to some sensitive ethical issues (25).

In the present study, in 50.4% of the articles evaluated (almost half) obtaining a consent form from the participants had been reported; however, Harrison reported a rate of 25.1%. Naraneetha reported a rate of 45.23% in author guide section of dental journals for a necessity to obtain ethics committee approval and a rate of 30.15% for obtaining consent forms from the subjects. Therefore, a sizeable proportion of valid dental journals ignore these two important ethical principles in author guide sections (13).

The results of this study showed that 99.5% of the articles had not mentioned the confidentiality of the personal information of the subjects. Ralenza and Cederbrg evaluated the issue from a different angle and reported that due to technological advances in recent years, electronic recording of personal data in dental centers has increased dramatically and it has become a more sensitive matter from the standpoint of ethical considerations to preserve a large amount of patient data (26).

An issue which has always been a matter for dissuasion is the fact that a clinical trial is considered "ethical" only when the clinician does not believe that one treatment modality is superior to the other one and since in fact each clinician trusts one treatment modality more than others the majority of RCTs are prone to being considered unethical. Johnson et al. estimated the permissible range of superiority of one treatment modality over another in order to determine a threshold for an RCT to be considered ethical. They reported a range of 70:30 for this threshold. In other words, they believed that it is not possible to implement full equality for the efficacy of two treatment modalities, which is considered an ideal (27).

The results of the present study showed that in the studies evaluated almost no attention had been paid to the rights of the subjects and to benefiting the participants; in fact, this is a very sensitive issue in some studies. For example, in a clinical trial in the US, the child participants had to travel from the school to the treatment center in a motor vehicle; Kipa and Leske reported that the methodology of the study exposed the children to traffic stresses during the study period (4).

In the present study in 65.3% of the RCTs evaluated, the methods used were completely safe for the participants. It should be pointed out that the rate mentioned above was not obtained using a definitive criterion and in the case of some methods cannot be considered completely safe. For example, use of radiographic techniques in RCTs has raised concerns due to the biologic effects of radiation. If such issues are considered from the viewpoint of benefits and losses, since radiation

hazards are cumulative, radiographic techniques should only be used in studies in which there is a definitive need for radiographic data (4). Another factor considered as unacceptable level in relation to the observance of ethical issues in the RCTs evaluated in the present study was an increase in the number of such studies in recent years. Bhan attributed a decrease in the observance of ethical guidelines in RCTs carried out in India to a dramatic increase in the number of such studies, making it difficult to monitor how well and ethically they are carried out (28). In the present study, no search was run to determine the correctness of the results of RCTs evaluated. However, based on a report by Slogging and Ramsey, of every 5 RCTs indexed in PubMed, only one full text is available (29). Therefore, it appears there is greater tendency to publish the results of RCTs, which have had positive conclusions and lack of access to the final data of all RCTs increases these doubts. Therefore, the necessity of registering all the RCTs should be pursued with more vigor. The ethical aspects of medical research studies are not confined to the points evaluated in the present study and reporting of the results of a study, management, and evaluation of its results are all integrated with ethical considerations; observance of all these issues requires the direct supervision and monitoring of all the research studies. In this respect, some unethical behaviors by some researchers, such as fabrication, falsification and plagiarism, exert irreparable detrimental effects on the integrity of research and it is not practical to extract such cases from the texts of published articles (30).

Barnett elaborated on the ethical aspects of those RCTs that are financially supported by commercial companies (31). In such cases, clinicians are paid by pharmaceutical companies to include patients in RCTs, which is not disclosed during the process of obtaining patient consent to participate in the study. It appears such issues are unethical and the patients have the right to be informed of such issues (32).

El-Dessouky et al. reported that 44% of the academic staff of dental faculties in Egypt and Saudi Arabia believed that the involvement of ethics committees in the research process resulted in a delay in research proceedings and only 40.2% had replied correctly to the ethical questions of research studies, which indicated the presence of a wide gap in knowledge about ethical issues in medical research (19). Some suggestions in relation to ethical issues include teaching of research ethical principles to post-graduate students in dental schools and faculties, holding annual congresses on research ethics, establishing committees to provide consultation on ethics for researchers and provision of more definite ethical codes for researchers through repeated revision of research ethics guidelines so that the present status can be improved (30). Lantz et al. reported a mean of 26.5 hours of instructions for ethical principles in 56 faculties evaluated and concluded that the medical ethics curricula in various faculties require revisions and corrections (33).

Singh and Purohit believe that teaching principles of ethics to dental students alone will not guarantee that these future researchers will observe these principles; therefore, the authoritative bodies that carry out grading of journals with criteria such as Impact Factor should consider better observance of ethical principles in articles published in different journals as a relevant factor during grading procedures. In addition, law-making bodies should pay more attention to ethical aspects in order to promote academic staff instead of considering the research itself as a tool for such purposes (34, 35). Observance of principles of ethics in dental RCTs should be taken more seriously than ever.

Conclusion

Most Iranian dental clinical trial reports failed to mention important ethical considerations such as ethical approval and informed consent. The reporting of the ethical issues associated with these trials should be improved further.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or

falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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