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Anja Engelking

THE USE OF SYSTEMATIC REVIEWS IN RANDOMIZED CONTROLLED TRIALS IN ANESTHESIOLOGY

Diploma thesis

Academic year:
2016/2017

Mentor:

Prof. Livia Puljak, MD, PhD

Split, June 2017

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1. INTRODUCTION

1.1. Pain

According to the taxonomy of International Association for the Study of Pain (IASP), pain is defined as an „unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”(1). Pain is a subjective feeling that each individual learns to express through different experiences in early life.

From a neurobiological perspective pain is three different things: Nociceptive pain, inflammatory pain and pathological pain (2).

Nociceptive pain represents an early-warning system essential to elicit the withdrawal reflex to protect oneself from damaging or noxious stimuli. The second kind of pain is inflammatory pain which is associated with tissue damage and the infiltration of immune cells. It is able to reduce further risk of damage and to promote recovery by causing hypersensitivity to pain until healing occurs. The last type is pathological pain which is maladaptive instead of protective and results from abnormal functioning of the nervous system rather than from actual tissue damage. Pathological pain can be divided further into neuropathic pain, caused by damage to the nervous system and dysfunctional pain, caused by conditions in which there is no damage of inflammation (exp. Tension type headache, irritable bowel syndrome) (2).

Pain can also be divided into acute and chronic states. While acute pain is self-limited and serves a biologic purpose, chronic pain may be considered a disease state. It outlasts the normal time of healing or arises from psychological states and has neither biologic purpose nor a recognizable end-point (3). Chronic pain is a major cause of suffering and disability worldwide, and a common symptom of both cancer and HIV/AIDS (4).

Pain has a profound impact on the quality of life and can have physical, psychological and social consequences (5). Because of that, according to the international human rights law, countries are obliged to provide pain treatment medications under the right to health (5).

1.2. Evidence-based medicine

Evidence-based medicine (EBM) integrates clinical expertise, patient's values and the best available evidence in the process of decision making related to patient health care (6).

The evidence is classified in a hierarchical system according to the probability of introduced bias.

Clinicians are encouraged to find the highest level of evidence to answer clinical questions. To facilitate the search for relevant data, papers are assigned a level of evidence to indicate their strength of recommendation. The grading system used may be different depending on the publishing journal, but most assign 4 or 5 levels, level 1 being the most recommended. Of course, this does not mean that all level 1 evidence should be accepted as fact, or that all level 4 evidence should be discarded. The ranking should be understood as a guide when interpreting study results (7).

According to the Centre for Evidence Based Medicine (CEBM) the most reliable evidence is provided by systematic reviews, summarizing the homogenous content of several randomized controlled trials (RCTs) and the least reliable source are case series studies and expert opinions, which are often heavily influenced by the authors' personal experiences and opinions (7).

1.3. Randomized controlled trials

RCTs are the most common type of experimental study in medicine and depending on the target population may aim to prevent or treat disease. They are the gold standard for studying efficacy and safety of new treatments and are indispensable for evidence based medicine (8).

Advantages of this study design are the high level of proof provided and the ability to study several outcomes at once. Unfortunately, the considerable amount of time and funding needed to complete an RCT is a major disadvantage and should make the researcher question the necessity of the information to be gained. Other disadvantages are the need for compliance of the participants, the possibility of a non-representative study population and patient comorbidities. RCTs are limited by ethical and practical concerns and the researcher should always question himself whether the intervention is well enough developed to permit evaluation and whether there is any preliminary evidence (observational studies) indicating that the intervention is likely to be beneficial (9).

Typical features of RCTs are the equal treatment of all intervention groups with the exception of the experimental treatment and the intention-to-treat analysis (all participants are analyzed within their allocated group irrespective of whether they experience the intended intervention) (9). A high quality RCT is determined by the choice of study question and design, as well as the prevention of systematic errors (bias). The avoidance of bias in RCTs is of great importance as it may easily falsify the results and thus decrease the level of evidence. This is usually achieved by randomization of the study population and the introduction of "blinding" into the study design. At the beginning of an RCT the population is sampled and randomly allocated into either experimental or control group. Random allocation ensures no systematic differences between groups in factors, whether known or unknown, that may affect the outcome (9). While both groups need to have comparable confounding factors, only the experimental group will be exposed to the therapeutic or preventive treatment being investigated. The control group on the other hand will receive the gold standard treatment, a placebo or no treatment at all (8).

"Blinding" is a procedure to keep study participants and sometimes the researcher (double blinding) unaware of the assigned intervention. Double blinding should be considered in studies, where the outcome may be subjectively influenced by the researchers' knowledge of what participants are receiving. Equally important is the adherence to ethical and legal requirements. It is essential that the researcher creates a structured RCT protocol describing the choice topic's background, risk-benefit assessment, study design and methods as well as the overall planning, conduct and analysis. The analysis in RCT is focused on estimating the size of the difference in predefined outcomes between the study arms (10).

1.4. Systematic reviews

Systematic reviews (SRs) provide the highest level of evidence, especially if they only include RCTs and contain meta-analysis. Lund et al. have recently provided updated definition of SRs, indicating that: "a systematic review is a structured and preplanned synthesis of original studies that consists of predefined research questions, inclusion criteria, search methods, selection procedures, quality assessment, data extraction, and data analysis" (11).

SRs are important tools to enable medical professionals to keep up with the

considerable and ever-growing amount of information published around the world. They provide a summary of the results of all individual primary studies on a given topic to increase the power of data. To produce a systematic review, it is necessary to apply certain inclusion and exclusion criteria for retrieved articles, to synthesize the extracted data and to formulate the findings. In the case of quantifiable and comparable data it is also possible to use statistical methods in order to pool the results of different studies and to form a meta-analysis (8).

The Cochrane is an international non-profit organization dedicated to making up-to-date, accurate information readily available worldwide, is the leading producer of systematic reviews (REF: www. cochrane.org). Cochrane systematic reviews are considered a 'gold standard' in evidence synthesis (12).

1.5. Waste in research

It has been reported that more than US$100 billion is invested every year around the globe in biomedical research, resulting in about 1 million research manuscripts per year. However, it was estimated in 2009 that as much as 85% of biomedical research funding was avoidably wasted (13). Regardless of who is funding research, this huge investment should be protected, and the concept of 'research waste' has recently gained international attention (13). Chalmers and Glasziou defined that waste occurs at four successive stages, including "the choice of research questions; the quality of research design and methods; the adequacy of publication practices; and the quality of reports of research" (13).

One of the problems emphasized along these stages is that researchers perform studies that are not necessary. It has been argued that new studies should not be conducted unless „at the time it is initiated, the questions it proposes to address cannot be answered satisfactorily with existing evidence"(13).

Number of biomedical studies is increasing on a massive scale. In 2013 there were 734,052 studies indexed in MEDLINE, and this number grew to 869,666 in year 2016 (14). SRs as original secondary studies that summarize and critically appraise existing evidence on a given topic can help users to find concise answers to their questions (15). High-quality systematic reviews can help in reducing research waste (12).

1.6. Use of systematic reviews in randomized controlled trials

RCTs should target new clinical questions, or seek to extend, confirm or reject previous research findings. Thus, before planning to conduct a new clinical trial, its authors should conduct a very thorough literature review and consult existing SRs on the subject (16).

In 2005 report of Cooper et al. described the study in which authors of trials added in the updates of Cochrane SRs were contacted and asked whether they used Cochrane or other SRs when they designed their study. Among 32 contacted authors 24 responded and of them 11 were aware of the relevant Cochrane SR at the time they designed their study (17).

In 2017 Rosenthal et al. reported analysis of 51 surgical trials, whereas 33 trials (65%) referenced a SR anywhere in a manuscript and 8 (16%) referenced it in the Introduction, but none of the analyzed RCTs indicated that the SR was used to inform design and conduct of the RCT. Two RCTs explicitly stated that their trial is the first in the field (16).

A framework for using SRs for designing primary studies suggested four steps, where first step is to formulate a clinical question and second step to find an up-to-date valid and relevant SR and to use it in the third step to inform study design (18).

Additionally, CONSORT statement, which was first published in 1996, urged clinical trialists to interpret data from a new trial “in the light of the totality of the available evidence” (19). Therefore, it is not only important to use SRs to inform design of a new trial, but also to discuss results in the context of previously existing SRs. Repeated analysis of RCTs published in major general biomedical journals indicated that few trials synthesize new findings in the light of previous findings and that apparently there is no progress over the years between 1998 and 2012 (20-24).

2. OBJECTIVES OF RESEARCH

The objective of this study was to analyze whether previous systematic reviews are mentioned in RCTs published in anesthesiology journals as a rationale for conducting the RCT and for discussing the results. We chose to analyze anesthesiology field because pain management is nowadays considered a fundamental human right. Therefore, it is an imperative to design and fund clinical trials in the field of anesthesiology and pain that are really necessary and informed by previous research results, and to put research results into the context.

The main hypothesis was that more than half of the analyzed RCTs did not mention in the introduction use of systematic reviews as a rationale for conducting the RCT.

The secondary hypotheses were:

- no RCTs mentioned systematic reviews as a justification in Methods,

- more than half of the analyzed RCTs did not mention any relevant systematic review on the subject in the Discussion

- more than half of the analyzed RCTs did not include a single systematic review in their list of references

- number of reviews cited as a justification for conducting a trial increased in the most recent years.

3. METHODS

3.1. Ethics

In this study data items from published RCTs were analyzed. Personal patient data were not included. Therefore, ethical committee approval was not sought.

3.2. Inclusion criteria

RCTs published between January 1, 2014 and December 31, 2016 in the first-quartile journals belonging to the Journal Citation Reports (JCR) category Anesthesiology were analyzed. Based on the 2014 JCR impact factor those were seven journals, including (in alphabetic order) *Anaesthesia*, *Anesthesia and Analgesia*, *Anesthesiology*, *Pain*, *British Journal of Anaesthesia*, *Pain Physician*, *Regional Anesthesia and Pain Medicine*.

3.3. Search

First, MEDLINE database was searched using advanced search feature with a journal name, with the following syntax: ("Anesthesiology"[Journal] OR "Pain"[Journal] OR "British journal of anaesthesia"[Journal] OR "Pain physician"[Journal] OR "Anesthesia and Analgesia"[Journal] OR "Anaesthesia"[Journal] OR "Regional anesthesia and pain medicine"[Journal]). Then we applied a filter for RCTs and a filter for publication dates January 1, 2014 to December 31, 2016. Bibliographic records (titles and abstracts) of retrieved search results were exported. Two authors independently screened bibliographic records to verify that those studies were indeed RCTs. When this was not clear from the title and abstracts, full texts of the manuscript were downloaded and two authors screened them independently. Disagreements were resolved via discussion between the authors or via involvement of a third author.

3.4. Data extraction

Data extraction table was prepared in the Microsoft Excel (Microsoft Inc., Redmond, WA, USA). The table was piloted with five abstracts; revisions were made if necessary.

Text and bibliography section of each RCT were analyzed. Introduction section was analyzed to see whether SR was mentioned to justify the research. Methods section was analyzed to see whether it was indicated that SR was used to inform trial design. Discussion section was analyzed to see whether any SR was mentioned when discussing synthesis of results, i.e. whether results of that new trial were put in the context of an existing SR on the topic. We indicated whether systematic review was explicitly mentioned as a justification, or simply as a reference. We noted how many systematic reviews were cited in the trial overall. Temporal trends were explored, i.e. did the number of trials citing systematic review(s) increase over the analyzed 3-year period.

3.5. Statistics

Descriptive data analysis was conducted using MedCalc statistical software, v 15.2.1 (MedCalc Software bvba, Ostend, Belgium). Data were presented as frequencies and percentages. Differences between the groups in the analysis of temporal trends were analyzed using one-way ANOVA after testing data for normality with Kolmogorov-Smirnov test. Statistical significance was set at $P < 0.05$.

4. RESULTS

4.1. Search results

After searching MEDLINE 668 bibliographic records were retrieved that were indexed as randomized controlled trials. After screening titles and abstracts 631 RCTs were included. For 37 articles it was not possible to judge whether those were indeed RCTs based on only titles and abstracts so those were screened in full text. Of those 37 records 13 were included because it was indicated in the methods that a study was randomized. We excluded 23 records because they were not RCTs and one because it was updated systematic review. Finally, the total number of included RCTs was 644. Among included RCTs there were two studies that were published only as letter to the editor and one manuscript that described two studies, one of which was RCT.

4.2. Usage of systematic reviews in Introduction

In 81/644 (13%) RCTs systematic review was explicitly mentioned (by words) in the Introduction. In 278/644 (43%) RCTs one or more SRs were cited as a reference in the Introduction. The majority cited only one SR, but two RCTs cited as many as 10 SRs. Table 1 shows how many SRs were mentioned in those RCTs.

Table 1. Number of systematic reviews cited in the Introduction of included randomized controlled trials

Number of systematic reviews cited	Number of randomized controlled trials (%)
1	128 (46)
2	76 (27)
3	39 (14)
4	18 (6.5)
5	9 (3.2)
6	3 (1.1)
7	2 (0.7)
8	1 (0.4)
9	1 (0.4)
10	2 (0.7)

Systematic reviews were cited as a justification for conducting that specific RCT in 76/633 (12%) cases.

4.3. Usage of systematic reviews in Methods

In 5/644 (0.8%) RCTs systematic review was explicitly mentioned (by words) in the Methods. In 51/644 (8%) RCTs one or more SRs were cited as a reference in the Methods. The majority cited only one SR, but one RCT cited as many as 4 SRs. Table 2 shows how many SRs were mentioned in those RCTs.

Table 2. Number of systematic reviews cited in the Methods of included randomized controlled trials

Number of systematic reviews cited	Number of randomized controlled trials (%)
1	40 (78)
2	7 (14)
3	3 (5.9)
4	1 (2.0)

Systematic reviews were cited as a justification for conducting that specific RCT in 2/642 (0.03%) cases; the remaining two RCTs were not formatted in a way to be divided into Introduction and Methods as separate sections.

4.4. Usage of systematic reviews in Discussion

In 245/644 (38%) RCTs systematic review was explicitly mentioned (by words) in the Discussion. In 242/644 (38%) RCTs one or more SRs were cited as a reference in the Discussion. The majority cited only one SR, but one RCT cited as many as 11 SRs. Table 3 shows how many SRs were mentioned in those RCTs.

Table 3. Number of systematic reviews cited in the Discussion of included randomized controlled trials

Number of systematic reviews cited	Number of randomized controlled trials (%)
1	129 (53)
2	53 (22)
3	27 (11)
4	13 (5.4)
5	7 (2.9)
6	4 (1.7)
7	5 (2.1)
8	1 (0.4)
9	2 (0.8)
11	1 (0.4)

Systematic reviews were cited as a justification for conducting that specific RCT in 62/644 (9.6%) cases.

4.5. Number of cited systematic reviews in the entire manuscript

Overall, almost half of the entire full text of the included RCTs (44%) did not mention a single systematic review, either in text explicitly or as a reference. Number of systematic reviews that were mentioned in the included RCTs is indicated in Table 4.

Table 4. Number of systematic reviews cited in entire included randomized controlled trials

Number of systematic reviews cited	Number of randomized controlled trials (%)
0	284 (44)
1	103 (16)
2	75 (12)
3	57 (8.9)
4	42 (6.5)
5	21 (3.3)
6	19 (3.0)
7	8 (1.2)
8	9 (1.4)
9	10 (1.6)
10	1 (0.2)
11	5 (0.8)
12	3 (0.5)
13	2 (0.3)
14	1 (0.2)
15	2 (0.3)
17	1 (0.2)
19	1 (0.2)

4.6. Temporal differences in number of mentioned systematic reviews

On average, there were 1.1 ± 0.3 SRs mentioned as a justification in introduction in year 2014, 1.1 ± 0.3 in 2015 and 1.2 ± 0.4 in 2016. There were no significant differences between the years (F=1.076, P=0.342).

Regarding number of SRs mentioned in the discussion of RCTs as a justification for conducting a trial, on average there were 1.1 ± 0.3 in 2014, 1.1 ± 0.3 in 2015 and 1.1 ± 0.3 in 2016. There were no significant differences between the years (F=2.067, P=0.127).

Among 251 RCTs published in 2014, on average there were 1.6 ± 1.3 SRs mentioned in the trial. Of 249 trials published in 2015 there were 2.0 ± 2.99 SRs mentioned in those trials, and of 144 trials published in 2016, there were 2.3 ± 3.1 SRs mentioned. This was a significant increase over the analyzed years (F = 3.73, P = 0.035).

5. DISCUSSION

The main finding of this study is that only about one tenth of the analyzed trials mentioned systematic review, either explicitly or only as a reference, as a justification for performing the trial in the introduction section. Few trials mentioned this justification in discussion section and only two in methods section. Analysis of temporal trends indicated that the number of trials that mentioned systematic review as a justification for conducting that trial in introduction or discussion did not increase from 2014 to 2016. However, a total number of cited systematic reviews in the analyzed trials significantly increased from 2014 to 2016.

RCTs are the best type of study design to assess the safety and efficacy of new treatments. They also form a necessary basis for approval decisions from governmental regulatory bodies (10).

A previous study emphasized the problem, that researchers perform studies that are not necessary and that new RCTs should only be conducted if at the time of its initiation, the proposed question has not been sufficiently answered by existing evidence (13). Considerable cost and time needs to be applied to complete an RCT and therefore it is unfortunate that the reported waste in biomedical research is 85%. This causes concerns when it comes to biomedical research funding and further highlights the importance of consulting pre-existing evidence before formulating a possible study question (9,13).

Systematic reviews are the most effective means of finding and appraising available evidence and are in conclusion also the best possible option to identify topics in need of further studies (25).

In order to evaluate the researcher's use of this existing evidence in choosing a research topic, we analyzed 644 RCTs from the field of anesthesiology published in seven different journals.

During the analysis, we found that only a minority of articles cited one or more systematic reviews as a justification for conducting that RCT. Almost half of the RCTs did not cite a single systematic review. The majority of the cited reviews were mentioned in the introduction of the article but in only 13% of cases they were used as an explanation for the trial's conduction.

The discussion sections of the texts mentioned almost as many SRs as the introductory parts with a similar lack of actual justifications. The method sections of the articles cited the least amount of pre-existing evidence. Only 51 out of all 644 articles mentioned even 1 systematic review. This was surprising, as this section is designed to describe how the study was planned and performed (8).

Clarke et al. collected data on clinical trial reports published in different years (1997, 2001, 2005 and 2009) and described the scarce citation of systematic reviews (23). They furthermore found no evidence of progress over the years, which seem to be a continuing trend, as shown in this study as well.

A descriptive cross-sectional study published in 2014, evaluating the use of systematic reviews in the field of dermatology noted a similar ignorance of available evidence. They analyzed a selection of trials from dermatology journals in 2010 and 2011 (25). Rosenthal et al. published a study in 2017, in which they reported that as 65% of the analyzed trial referenced one or more systematic reviews, 16% referenced one or more systematic reviews in the introduction, but none of them was used explicitly to justify the conduct of that trial. However, that study included all 2010 issues of Annals of Surgery, JAMA Surgery, and British Journal of Surgery, so the study is referring to older trials even though it was published in 2015 (16).

It is encouraging that this analysis showed that number of overall cited systematic reviews increased from 2014 to 2016, although not to justify the conduct of a trial. This is perhaps the next step.

A limitation of this study is reliance on only one database. It can be argued that there are many bibliographic databases that could be searched to find relevant trials and it has been said that none of the existing databases can be considered completely comprehensive (26). Some journals are indexed only in one database. However, recent methodological research findings indicate that searching only MEDLINE is cost-effective approach and that 89% of the relevant trials can be found in MEDLINE, except for psychiatric and psychology fields (27). Furthermore, one limitation is limited time-frame. However, since there are already several studies published about similar topic, albeit in different research fields, the aim of this study was to analyze only the most recent trials.

Future studies should be aimed towards interventions that can be used to remedy this situation and reduce research waste. Ethics committees should ask for justification based on previous systematic review(s) of literature when a group of researchers submits new RCT for approval. Authors of relevant checklist for conducting primary studies need to include justification based on a previous literature as one of the obligatory reporting items. Journal editors and peer-reviewers should pay attention to this reporting item and ask authors to cite relevant previous systematic review(s) or their own literature synthesis as justification for their trial. Also, a new line of research should involve trial authors, and to explore did they even consult any relevant systematic reviews, and perhaps simply failed to report it, or they did not pay attention to existing evidence synthesis when designing their own trial.

These findings demonstrate the fact that even with the increasing amount of available systematic reviews and Cochrane reviews and especially with several previous studies from different research fields showing the lack of their consideration in the choice of study questions has been known, the same can be said for trials conducted in the field of anesthesiology and pain. Still it is necessary to keep emphasizing the importance of the use of systematic review for justifying new trials in order to minimize the overwhelming waste of research funding.

6. CONCLUSIONS

Conclusions of this study are the following:

- There were 13% of the trials that were justified with mention of a systematic review in introduction.

- In only 0.03% of trials justification for conducting the trial, in terms of a previous systematic review, was mentioned in the methods.

- There were 9.6% of trials that were justified in discussion by citing formerly conducted systematic review.

- Analysis of temporal trends indicated that the number of trials that mentioned systematic review as a justification for conducting that trial in introduction or discussion did not increase from 2014 to 2016. However, a total number of cited systematic reviews in the analyzed trials significantly increased from 2014 to 2016.

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8. SUMMARY

Objectives: Systematic reviews (SRs) summarize current knowledge on a certain clinical question. To avoid research waste, new randomized clinical trials (RCTs) should be initiated if previous SRs indicate that there is no such evidence or that there is insufficient evidence from previous RCTs. The objective of this study was to analyze whether previous SRs are mentioned in RCTs published in anesthesiology journals as a rationale for conducting the RCT and for discussing the results.

Methods: This was a meta-epidemiological, descriptive cross-sectional study. We analyzed RCTs published in the seven first-quartile journals from the Journal Citation Reports (JCR) category Anesthesiology between 2014 and 2016. We studied text and bibliography of the RCTs to assess whether the authors made a reference to previous SRs when justifying the need for their own clinical trial and discussing the results.

Results: Almost half of the included RCTs (44%) did not mention a single systematic review, either in text explicitly or as a reference. Around 10% of the included RCTs mentioned a previous systematic review as a justification for conducting a trial. Between 2014 and 2016 we noted no significant difference in the number of SRs mentioned as a justification in introduction or discussion but the total number of SRs mentioned increased significantly (F= 3.73, P= 0.035).

Conclusions: Although an increase of total mentions of systematic reviews was observed, the percentage of articles that actually used them to justify their trials did not change significantly.

9. SUMMARY (CROATIAN)

Naslov: Uporaba sustavnih pregleda u randomiziranim kontroliranim pokusima iz anesteziologije

Ciljevi: Sustavni pregledi sažimaju trenutno znanje o pojedinim kliničkim pitanjima. Kako bi se izbjeglo razbacivanje istraživačkim resursima novi randomizirani klinički pokusi trebali bi se provoditi samo ako raniji sustavni pregledi pokazuju da nema dovoljno takvih dokaza ili da ranije provedeni klinički pokusi ne sadrže dostatne dokaze. Cilj ovog istraživanja bio je analizirati spominju li se raniji sustavni pregledi u radovima koji opisuju kliničke pokuse kao opravdanje za provedbu tog pokusa i za diskutiranje rezultata.

Metode: Provedeno je metodološko presječno istraživanje. Analizirani su randomizirani klinički pokusi objavljeni od 2014. do 2016. u sedam časopisa iz prve kvartile u *Journal Citation Reports* (JCR) kategoriji iz područja anesteziologije. Analiziran je tekst i bibliografija kliničkog pokusa kako bi se utvrdilo spominju li se sustavni pregledi eksplicitno ili samo kao referenca, i spominju li se kao razlog zašto je potreban novi klinički pokus.

Rezultati: Gotovo polovina uključenih kliničkih pokusa (44%) nije citirala niti jedan sustavni pregled, ili eksplicitno u tekstu ili kao referencu. Samo 13% analiziranih kliničkih pokusa spomenulo je raniji sustavni pregled kao opravdanje za provedbu pokusa u uvodu, 0,03% u metodama i 9,6% u raspravi. Između 2014. i 2016. godine nije uočeno značajno povećanje spominjanja sustavnih pregleda kao opravdanja za korištenje kliničkog pokusa, ali je uočeno značajno povećanje broja citiranih sustavnih pregleda ($F= 3.73$, $P= 0.035$).

Zaključak: Iako je uočeno povećanje broja citiranih sustavnih pregleda u analiziranom razdoblju, postotak kliničkih pokusa koji koriste te sustavne preglede kao opravdanje za provedbu kliničkog pokusa još uvijek je vrlo nizak. Nužno je provesti intervencije koje će povećati svijest autora kliničkih pokusa o potrebi provedbe kliničkog pokusa jedino ako ta potreba zaista postoji temeljem ranije sinteze literature, a isto tako o potrebi citiranja sinteze literature na kojoj se potreba za novim kliničkim pokusom temelji.

10. CURRICULUM VITAE

Personal Information

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Education

Since October 2011: Medical Studies at the University of Split, School of Medicine

September 2010 – November 2010: Apprenticeship as Emergency medical technician with the German Red Cross in Olpe

2007 – 2010: Dietrich-Bonhoeffer-Gymnasium (secondary school) in Wiehl

2001 – 2007: Realschule (secondary school) in Wiehl

1997 – 2001: Primary school in Wiehl

Other Activities

2011: Work as an ambulance car driver at the fire station of Wermelskirchen

April 2011 – May 2011: Nurse internship in the St. Josef-Hospital in Engelskirchen

March 2011: Nurse internship in the Herz-Jesu-Hospital in Lindlar

2011: Voluntary work for the Johanniter Emergency care as an Emergency medical technician

September 2010 – Oktober 2010: Internship in Kreiskrankenhaus in Waldbröl