Reporting of sex and race/ethnicity in randomized controlled trials of interventions published in the top journals from the field of anesthesiology and pain

Janda-Martinac, Clemens Jan

Master's thesis / Diplomski rad

2018

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:171:684195

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Clemens Janda-Martinac

Reporting of sex and race/ethnicity in randomized controlled trials of interventions published in the top journals from the field of anesthesiology and pain

Diploma thesis

Academic year:

2017/2018

Mentor:

Assoc. Prof. Livia Puljak, MD, PhD

Split, July 2018

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

Clemens Janda-Martinac

Reporting of sex and race/ethnicity in randomized controlled trials of interventions published in the top journals from the field of anesthesiology and pain

Diploma thesis

Academic year:

2017/2018

Mentor:

Assoc. Prof. Livia Puljak, MD, PhD

Split, July 2018

Table of contents

ACKNOWLEDGEMENTS

First of all, I want to thank my mentor Livia Puljak, MD, PhD for all the help and support for finishing my diploma thesis. Thank you for always answering immediately and solving any problem during the past months. And also thank you for being as nice as you are and for motivating me.

Mein nächster Dank geht an all meine Freunde aus Düsseldorf. Tobi, Fabio, Dän, Dome, Choffer, Kevin, Vla, Salva, Marc, Philipp und einfach alle anderen, danke dafür, dass es euch gibt und ich mit euch als Freunden diesen Weg gehen konnte. Und Tobi, auch dich wird Split vermissen.

Nicht weniger möchte ich allen Leuten aus Split danken, die hier für mich da waren, sowohl Andre, Johanna, Anja, als auch das „neue Jahr". Danke, dass ich mich bei euch so wohl fühlen konnte. Vor allem an Gundi, Tim, Lorenz, Ihr habt mir die letzten Monate perfekt gemacht. Natürlich Fritzi, du bist der Beste, zieh das Ding durch. Und Josi und Daniel auch ihr habt mir die Zeit hier unvergesslich gemacht. Danke auch an all den Rest und für viele neue Freundschaften.

Ante, I know you gonna hate that cheesy part, but thank you for being there for me every single day at Krabbe, for all the Narančadas and Bijelas. But most important for being you and for being a friend. You are the best. And thank you to Tanja and Lukas for every lunch you invited me and just for everything. I will miss you.

Aber das wichtigste aus Split ist natürlich Yassi. Ich danke dir einfach für alles. Ohne dich wäre Split nicht das geworden, was es für mich ist. Danke, für all die schönen Momente, diese einfach unvergessliche Zeit mit dir und die Unterstützung die ich jeden Tag von dir bekommen durfte. Ich bin so froh, dass wir das jetzt weiterführen können. Ich liebe dich.

Am meisten Danke ich meiner Familie. Oma, Opa, Bene, Karen, Mama, Papa, Stephan und Moni. Ich danke euch einfach für alles. Ohne eure emotionale Unterstützung, wenn es mal nicht so gut lief, hätte ich das alles nie geschafft. Ihr seid immer für mich da und wart das mein Leben lang. Ich danke euch dafür, dass Ihr mich zu dem gemacht hab was ich heute bin. Ich bin stolz euch alle zu haben. Ich liebe euch.

1. INTRODUCTION

1.1. Pain

Conferring 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 an individual feeling that each individual understands to express through different experiences in early life. From a neurobiological standpoint pain is divided in three different categories: nociceptive pain, inflammatory pain and pathological pain (2).

Nociceptive pain is an early-warning system crucial to stimulate the withdrawal reflex to protect oneself from damaging or noxious stimuli. The second type of pain is inflammatory pain which is connected with tissue damage and the infiltration of immune cells. It reduces further risk of damage and promotes recovery by causing hypersensitivity to pain until healing occurs. The final type is pathological pain, which does not protect but is maladaptive and results from abnormal functioning of the nervous system rather than from actual tissue damage. Pathological pain is caused by conditions in which no damage of inflammation is the cause but is provoked by damage to the nervous system. This is why it can be divided in neuropathic pain and dysfunctional pain (2).

Temporal classification divides pain into acute and chronic. It is considered that acute pain lasts up to three months, and chronic pain more than three months. As acute pain is self-limited and serves a biologic purpose, chronic pain could be considered a disease state. It endures the normal period of healing or develops from psychological states and has neither biologic purpose nor an identifiable end-point (3). Chronic pain is main cause of suffering and disability worldwide, and a usual symptom of many diseases that interfere with life quality (4).

As pain has an intense influence on the quality of life it can have physical, psychological and social effects (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. Hierarchy of evidence based medicine

In order to make decisions about the care and health of patients, evidence-based medicine is the key to refer on. It is the careful, precise, wise and rational use of new and modern use of making decision about management of patients (6).

Evidence based medicine combines clinical experience of healthcare workers and patient values with the best available research information. The aim is to increase the quality

of using scientific research in making decisions in clinical settings. For healthcare workers it is crucial to be skilled in literature-searching and evidence appraisal so that they can incorporate best available evidence in their clinical practice (6).

A great benefit of evidence-based medicine has been the development of systematic reviews and meta-analyses, methods where multiple studies on a topic were identified, then the best ones are evaluated to analyze them in a robust and rigorous way to create a summary of the best available evidence (6).

Evidence-based medicine classifies different types in a hierarchical system of clinical evidence and is then classified conferring to the potency of their choice from the various biases that affected medical research (6).

Level 1 stands for evidence obtained by meta-analysis of several randomized controlled trials (RCTs). Evidence from only one RCT is considered as level 1b while evidence from well-designed controlled trial is level 2a. Furthermore, evidence from one experimental research are level 2b. The next is level 3, which contains evidence from non-experimental studies as comparative research or case studies, according to for example textbooks. Evidence based solely on expert opinion and impressions from clinical practice are described as level 4 (6).

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 specify their strength of recommendation. The grading system used may be different depending on the publishing journal, but most allocate 4 or 5 levels, level 1 being the most recommended. Obviously, this does not mean that all level 1 evidence should be accepted as fact, or that all level 4 evidence should be unnecessary. The ranking should be taken as a direction when interpreting study results (7).

Nowadays, it is expected that all physicians in western countries apply evidence-based medicine in management for every patient, which is supported by the governments of these countries, the ministries of health and pharmaceutical industry. This practice incorporates evidence-based clinical guidelines for different diseases, which is a database with the best given evidence from each category that is updated every day with the newest information (6).

The Centre for Evidence Based Medicine (CEBM) states that the most reliable evidence is found in systematic reviews, types of research that summarize evidence from other studies. To the contrary, the least reliable sources are case series studies and expert opinions, because they often contain the authors' personal experiences and opinions (7).

1.3. Randomized controlled trials

RCTs are considered as highest-ranking primary studies in the hierarchy of evidence in medicine. RCTs can be used to study interventions that prevent or treat a disease. They are vital for evidence-based medicine as they are the gold standard for studying efficacy and safety of new treatments (8).

One decisive advantage of RCTs over non-randomized studies for the evaluation of therapeutic procedures is randomization which gives participants equal opportunity that they will be in any of the RCT arms. When starting an RCT the population is sampled and randomly assigned into either experimental or control group. By this distribution, systematic differences between groups in factors are prevented, whether known or unknown, that may affect the outcome. Therefore, it is expected that the groups show the same number of desired or undesired events over the study period, assumed they received the same treatment (9).

Typical features of RCTs are that all intervention groups are treated equal except of the experimental treatment and the intention-to-treat analysis what means that all participants are analyzed within their allocated group irrespective of whether they experience the intended intervention (10). To ensure a standard of a high quality RCT, the choice of study question and design plays an important role, as well as the prevention of systematic errors. Bias in RCTs is of great importance, and therefore planning of trial has to be very meticulous in order to avoid bias, because bias easily falsifies the results and may decrease the level of evidence. This can be circumvented by proper randomization of the study population, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, making sure that all data planned in the protocol are reported, that all participants lost to follow-up are accounted for, and that there are no other known sources of bias (10).

Another big advantages of RCT study design are the high level of proof provided and the ability to study several outcomes at once. On the other hand the amount of time that needs to be spent and the costs that it takes to complete a RCT is a major disadvantage. Therefore the researcher has to be aware of the necessity of the results at the end of the study and the costs that will emerge (10). Other disadvantages are the need for compliance of the participants. Also the possibility of a non-representative study population and patient comorbidities are factors that need to be considered. RCTs are limited by ethical and practical concerns. The researcher should always question him whether the intervention is likely to be beneficial. It is important to know if the treatment is developed well enough to permit evaluation (10).

Only the experimental group will be able to receive the therapeutic or preventive treatment being investigated. The control group contrary will receive the gold standard treatment, or even a placebo or no treatment at all (8).

By blinding study participants and if double blinding also the researcher are unaware of the assigned intervention. Double blinding is of advantage, in studies where the outcome may be influenced if the researcher knows about the distribution of experimental - or control group and of what participants are receiving (11).

Ethical and legal requirements are equally important. The researcher has to create a planned RCT protocol describing the choice topic's background, risk-benefit assessment, study design and methods and analysis. The analysis in RCT is aimed on approximating the size of the alteration in predefined outcomes between the study arms (11).

Latest discussions in worldwide scientific communities, which regulate the use of drugs and medical devices, show that RCTs are still the standard for validating efficacy and safety so that a new management and intervention can be accepted for use in patients (11).

1.4. Reporting of sex/gender and race/ethnicity in trials

Importance of the role of sex and ethnicity in pathology, diagnosis, prevention and treatment of diseases has been increasingly emphasized in the scientific community. This increased attention to sex-related differences apparently has led to modest increase of inclusion of both sexes and reporting of sex-specific analyses in randomized controlled trials (RCTs). Analysis conducted in trials published in nine prominent medical journals in 2009 showed that median proportion of women in trials that included both men and women was 37% (12). In 2016 such analysis of trials published in two prominent journals showed that this proportion was 41% (13). A 2009 study showed that 75% of trials did not have any outcome analyses based on sex (12), while the 2016 study did not find a single trial that had pre-specified analysis of differences by sex (13).

Similar lack of attention to race/ethnicity was found. A 2009 study indicated that 21% of trials did not report race or ethnicity of their sample, and 64% did not do any analyses based on race/ethnicity (12). In the field of pain, influence of sex on experimentally-induced pain and pain sensitivity is still the subject of debate (14,15).

However, lack of attention to sex-related reporting in clinical trials about pain has been noted

in recent literature. A systematic review about sex differences in the efficacy of psychological therapies for treatment of chronic and recurrent pain in children and adolescents found that not a single study published on the subject reported outcome data separately by sex. So, systematic review authors contacted authors of 46 included studies and 17 studies provided data (16). The review conclusion was that future studies need to examine whether mechanisms of treatment efficacy differ between sexes, and consider the impact of pre-treatment sex differences on response to treatment (16). Insufficient reporting of sex effects was also found for systematic reviews about chronic pain (17).

Multiple studies in the past have already shown that there is a high amount of chronic pain states and greater pain sensitivity among females compared to males. Pain is thought to be mediated by many different compounds. Therefore the sex differences should be emphasized (18). A factor that also needs to be included are sex hormones. They play a big role in the influence of pain sensitivity. Especially the menstrual cycle in females changes the threshold and tolerance of pain (18).

Likewise, many studies reported that race/ethnicity is associated with important differences between patients when it comes to pain. For this reason, race/ethnicity should be reported among the baseline characteristics of patients and, when feasible, outcomes should also be reported per race/ethnicity so that we can gain more insight into potential differences in the effect of interventions related to race/ethnicity (19–21). The important role of comorbidities in different races was shown in hospital readmission. It presented that there are higher rates of readmission in black people than in white associated with chest pain. That leads to the suggestion that biological and genetic factors play a role in racial disproportions.

That gene variations could lead to bigger problems as it has to be known that many diseases show different signs and symptoms and are expressed differently intensity in different races. Therefore it might be that the patient has to be individually treated by taking this fact into account (20).

Regarding diseases and their symptoms and outcomes it is necessary to report about the gender distribution. For example, it is shown that women in early stages of coronary artery disease present with symptoms such as fatigue, abdominal discomfort, back pain or neck pain. The problem here is that all of those symptoms are considered to be atypical, as those are standards which were mainly researched on men (22). Furthermore, usual tests that are used for diagnosis, like electrocardiography and radionucleotide myocardial perfusion imaging are

not as sensitive to detect coronary artery disease in women as in men. Studies on mice about gene constitution, presented different expression of genes in multiple tissues that are differently manifested in males than in females. Additionally there are hereditary differences of hormonal action depending if the mother or the father inherits it (22).

Clinical experience shows that men and women react differently on certain drugs and medication. One crucial example is that anesthesiologists found out that women awake much faster from sedation from propofol then men. On the other hand men have a shorter recovery time whereas women are more prone to get side effects like nausea and vomiting or headache. This is why anesthesiologists had to learn to calculate the dosage taking into account patients gender and the women's stage of menstrual cycle (22).

These circumstances warrant increased scrutiny of gender-based bias in clinical research. Otherwise women will face the problem of getting therapies, which may not be of the same benefit as they are for men (22).

2. OBJECTIVES

The aim of this study was to assess reporting of data on sex and race/ethnicity in RCTs of interventions published in the highest-ranking journals from the field of anaesthesiology from 2014 to 2017. Specific aims of the study were to analyse

(i) whether stratification based on sex and race/ethnicity was specified in methods,
(ii) the proportion of women vs men participants included,
(iii) the proportion of participants of different ethnicity included,
(iv) whether sex-related or race/ethnicity-related results were reported (either as a subgroup analysis for any outcome, or as a covariate in modeling),
(v) whether there was any difference in efficacy of tested interventions related to sex and race/ethnicity and
(vi) whether sex-related or race/ethnicity results were addressed in Discussion.

The hypotheses for the analysed cohort of trials were:

(i) less than 10% of analyzed trials will include stratification based on sex and race/ethnicity
(ii) proportion of included women will be significantly lower compared to proportion of men
(iii) less than 10% of analyzed trial reported information about participants' ethnicity
(iv) sex-related or race/ethnicity-related results were reported in less than 10% of analyzed trials
(v) if tested, majority of trails will show significant differences in efficacy of tested interventions related to sex and race/ethnicity
(vi) less than 10% of analyzed trials addressed sex-related or race/ethnicity in Discussion.

3. MATERIALS AND METHODS

3.1. Study design

This was a cross-sectional meta-epidemiological study of RCTs published in peer-reviewed journals. We conducted only analysis of publicly available secondary data; personal patient data were not included and therefore approval of an Ethics committee was not necessary.

3.2. Inclusion and exclusion criteria

We included RCTs of interventions that were published during the most recent full four years in the first-quartile journals indexed in the Journal Citation Reports (JCR) category *Anesthesiology*. Based on the 2016 JCR impact factor those seven journals were (in alphabetic order) *Anaesthesia*, *Anesthesia and Analgesia*, *Anesthesiology*, *Pain*, *British Journal of Anaesthesia*, *European Journal of Anaesthesiology*, *Regional Anesthesia and Pain Medicine*.

3.3. Search

We searched MEDLINE using advanced search feature with a journal name, filter for trials and filter for the chosen dates. We exported bibliographic records (titles and abstracts) of search results to EndNote X5 (Clarivate Analytics) reference management software. The authors independently screened titles/abstracts and full texts if necessary against inclusion criteria. Any disagreements were resolved via discussion. Full texts of included trials were downloaded for data extraction.

3.4. Data extraction

We used Microsoft Excel (Microsoft Inc., Redmond, WA, USA) to prepare data extraction sheets, which were piloted on ten first studies for consistency and clarity. We extracted the following data: name of the study, year of publication, journal name, availability of stratification based on sex and race/ethnicity in methods, number of men and women enrolled, number of members of different race/ethnicity enrolled, pre-specification of sex-related or race/ethnicity related analyses in methods, presence of sex-related or race/ethnicity related analyses in results, type of analysis planned, type of analysis reported, numerical data about differences in efficacy of tested interventions related to sex and race/ethnicity and presence of information about sex-related or race/ethnicity results in discussion. We explored

temporal trends to see whether any of the analyzed data occurred with higher frequency in the more recent years over the analyzed period.

3.5. Data analysis

We used MedCalc statistical software, v 15.2.1 (MedCalc Software bvba, Ostend, Belgium) to conduct data analysis. We presented descriptive statistics data as frequencies and percentages.

4. RESULTS

We analyzed 657 RCTs published between 2014 and mid-2017. The majority of RCTs were published in the journal Anesthesia & Analgesia (N=124, 19%), followed by British Journal of Anesthesiology (N=105, 16%), Pain (N=102, 16%), Anesthesiology (N=95, 14%), Anaesthesia (N=86, 13%), European Journal of Anaesthesiology (N=83, 13%) and Regional Anaesthesia and Pain Medicine (N=62, 9 %).

In our sample of RCTs there were 82 (12%) trials that specified they included exclusively women or men: 61 of which indicated they included only women and 21 included only men. Among those 61 studies that included women only there were 26 related to pregnancy and childbirth, 3 about mastectomy, 16 about gynecological surgeries. The rest of 16 trials that included exclusively women only mentioned that men were not included without a specific reason.

Among 22 studies that specified they included only men there was 1 article about opioid- induced hyperalgesia, where authors stated that the reason for excluding women is due to variations during female menstrual cycle, 1 article was about hypospadias of the male urethra, 1 paper focused on prostatectomy and all the other 19 men-specific trials did not declare a specific reason for that.

4.1. Terminology

When we analyzed sex vs. gender terminology, 253 (36%) trials mentioned one of these two words. Among them, 177 (75%) used word sex, while 61 (25%) used word gender. Not a single trial used both of those words in the manuscript.

Terminology used in the analyzed trials for men was: male (N=427, 65%), men (N=20, 3%), or the authors simply used letter M (N=32, 5%), while men-related words were not used in 177 trials (27%).

Terminology used for women in trials was: female (N=417, 63%), women (N=55, 8%), or just letter F (N=30, 5%); in 172 trials (23%) authors did not use any words related to women.

4.2. Reporting and analyzing sex/gender

In 18 (2.7%) studies the authors mentioned sex/gender terms in Background/Introduction section of the manuscript. In 53 (8%) studies the authors mentioned sex/gender terms in Inclusion/exclusion criteria. Analyses of sex/gender was planned in

Methods in 32 (5%) of the analyzed trials. In 52 (7.9%) trials authors reported in Results data for at least one analyses related to sex/gender. There were 27 (4%) trials that mentioned sex/gender in the Discussion section.

4.3. Reporting race/ethnicity

Regarding the analyses of reporting the race or ethnicity of the patients, we found out that out of 657 trials, authors of 59 (9%) mentioned participants' race or ethnicity anywhere in the manuscript. In 3 (0.4%) of studies the authors mentioned race/ethnicity in Background/Introduction section. In 6 (0.9%) trials the authors mentioned race/ethnicity in inclusion/exclusion criteria. There were 5 (1%) trials that planned any analyses related to race/ethnicity in Methods. In 8 (1.2%) trials authors reported any kind of analyses about race/ethnicity in the Results section, whereas 5 (1%) of trials mentioned anything related to race/ethnicity in their Discussion section.

4.4. Proportion of women and men in trials that included both sexes

Among 657 RCTs, there were 417 (63%) that included both men and women and reported number of participants according to sex. In those trials, on average, there were 49% (range: 2.1 to 98%) of men and 51% (range: 2.5 to 98%) of women. Since there were 82 trials that specified they included only participants of one sex, there were 158 (24%) trials that either did not report whether they included both women and men, or they did not report number of women and men in a trial.

4.5. Proportion of race/ethnicity

There were 59 (9%) of trials that reported any information about proportion of participants according to race/ethnicity. Three among them included only white participants, and one included only African American participants. In 34 of those 59 trials participants belonged to three or more races; 5 included white and African American participants. In 15 trials authors mentioned that some participants belonged to certain race/ethnicity, but without specifying this information for the remaining participants. In one study the authors indicated that the participants were born in Denmark, but without information about race/ethnicity.

Average percent of white participants in the 59 studies that reported any information about race/ethnicity was 74% (range: 2.4% to 100%). In 6 (10%) out of 59 studies the reported number of participants of different race/ethnicity did not match the total number of included participants; therefore, the authors have probably made mistakes while listing the number of participants of different race/ethnicity.

4.6. Results of sex-based analyses, and race/ethnicity-based analyses

In 52 (7.9%) trials that reported results of sex-based analyses in Results, 20 (38%) described that there was a significant difference between women and men in at least one analyzed outcome. Table 1 shows examples of results that explored study outcomes in the context of sex/gender. Among 8 trials that reported results based on race/ethnicity, 1 (12.5%) trial reported significant difference in at least one analyzed outcome for participants of different race/ethnicity. There were no trials that reported stratification of participants according to the sex/gender or race/ethnicity. Examples of reported results for study outcomes according to the race/ethnicity are shown in Table 2.

Table 1. Example of results reported for analyses related to sex/gender

Results	Significant difference based on sex/gender?
A Cox proportional hazards model for the time to the first analgesic request was performed including the following variables: dexamethasone dose, **sex**, age and type of surgery. None of the variables except dose of dexamethasone was significant (Fig. 2).	No
Additionally, analyses were conducted in both the TKR and THR cohort to explore the interaction of **gender** with preoperative pain severity, change in pain severity, PPTs and preoperative pain severity, and PPTs and change in pain severity. No strong evidence of an interaction was observed (data not shown).	No
Factors that were not associated with posterior vessel wall puncture included **sex**, experience in practice, specialty, and the number of ultrasound-guided vascular access procedures performed or supervised (table 2).	No
Among the 67 patients in Group I, 11 men and two women received IOC versus 18 men and 20 women among the 71 patients in Group C. There were statistically significant effects of mobilisation on both men and women, but **more men than women** in Group I required IOC ($P<0.04$).	Yes
Analyses of SPID48 based on **sex**, age, body mass index (BMI), and type of surgery were statistically significantly greater for SSTS compared with placebo for all subgroups ($P < 0.001$; table 2).	Yes
At mid levels, significant predictors were BMI, **sex** and intervertebral space ($R2=0.21$; $P<0.001$), whereas at low levels only weight as significant ($R2=0.34$; $P<0.001$).	Yes

Table 2. Example of results reported for analyses related to race/ethnicity

Results	Significant difference based on race/ethnicity?
Asian patients were not at an increased risk of PONV, despite being less likely to receive PONV prophylaxis (Supplemental Digital Content 1, table 3, http://links.lww.com/ALN/B260).	No
Covariates for this outcome included sex, race/ethnicity, education, income, and number of medical comorbidities. There was no significant effect of treatment, F(1,102) 5 1.55, P 5 0.216. Furthermore, the time by treatment interaction was not significant, F(2,207) 5 0.06, P 5 0.9376, nor were any interactions between the covariates and treatment condition.	No
Sex, race/ethnicity, and BMI were not significant moderators for any of the outcomes.	No
When age, gender, race, education, BMI, and treatment severity were added as covariates, the effect for psychological distress trended (p = .095) at post-treatment. The effect for satisfaction with health also trended (p = .083) at 6-month follow-up and was significant (p = .047) at 12-month follow-up.	No
Compared with White, Hispanics were associated with significant higher motor strength (P = 0.011), while Other patients (unknown ethnicity) were associated with significantly lower motor strength (P = 0.015).	Yes

5. DISCUSSION

In this study we found that less than ten percent of analyzed randomized controlled trials reported results for sex-related analysis and one percent reported race/ethnicity-related analyses in their results. When trials included both women and men, and reported number of participants according to the sex, on average, there were more men included in trials, but with no major differences overall, as percent of women vs. men in trials was 51% vs. 49%, respectively. A quarter of trial authors used word gender instead of sex, and the majority of trials used words female and male, compared to women and men. In 38% of studies that reported outcomes for sex-related differences the study showed that there were significant differences between women and men for at least one outcome.

Importance of the role of sex and ethnicity in pathology, diagnosis, prevention and treatment of various health conditions has been increasingly recognized as important in the scientific community. This increased attention to sex-related differences apparently has led to modest increase of inclusion of both sexes and reporting of sex-specific analyses in randomized controlled trials (RCTs). Analysis conducted in trials published in nine prominent medical journals in 2009 showed that median proportion of women in trials that included both men and women was 37% (12). In 2016 such analysis of trials published in two prominent journals showed that this proportion of women was 41% (13). In our study, we found that proportion of women was just slightly higher, i.e. 51%.

A study of Geller et al. from 2011, analyzed RCTs published in nine prominent medical journals in 2009, and showed that 75% of trials did not have any outcome analyses based on sex (12). Avery et al. analyzed RCTs published in two journals with high impact, The Lancet and New England Journal of Medicine (NEJM), between April 1, 2016, and July 16, 2016. They found 60 trials, excluding nine that analyzed sex-specific conditions. They did not find a single trial that had pre-specified analysis of differences by sex (13).

A study from 2017 of Welch et al. analyzed reporting about sex and/or gender in a sample of RCTs conducted in Canada on humans. The study showed that 98% of the trials they analyzed, described the demographics of the participants, while only 6% accompanied a subgroup about sex, whereas none of that trials reported any comprehensive analysis about sex or gender (23).

Additionally, the authors reported about the terminology that was used to describe the patients' demographic composition. The variations of using the term sex or gender was big,

while no RCT gave a definition of sex or gender. Likewise, none of the trials explained any intention to conduct or specify gender or sex analysis (23).

In our study we did not analyze trial protocols, so we cannot make any conclusions about whether our included trials perhaps planned to do sex-specific analyses, but failed to report them subsequently. We only analyzed information that were available in a manuscript published in the analyzed journals. Based on our results, there were 32 trials that mentioned sex-based analyses in Methods, and 52 that reported any sex-related analyses.

In the field of pain, influence of sex on experimentally-induced pain and pain sensitivity is still debated (14,15). However, insufficient attention to sex-related reporting in clinical trials about pain has been highlighted in recent literature. A systematic review about sex differences in the efficacy of psychological therapies for treatment of chronic and recurrent pain in children and adolescents found that not a single study published on this subject reported outcome data separately by sex. To obtain these data, authors of the systematic review contacted authors of 46 included studies and authors of 17 studies provided requested data (16). The systematic review conclusion was that future studies need to examine whether mechanisms of treatment efficacy differ between sexes, and consider the impact of pre-treatment sex differences on response to treatment (16).

Insufficient reporting of sex effects was also found for systematic reviews (SRs) about chronic pain (17). Duan-Porter et al. analyzed SRs on interventions for treatment of depression, type 2 diabetes mellitus, and chronic pain conditions, where pain conditions included chronic low back pain, knee osteoarthritis, and fibromyalgia. The study included SRs published since October 1st, 2009 that analyzed medications, behavioral interventions, exercise, quality improvement, and some condition-specific treatments. Reporting of sex effects by primary RCTs was also examined. Among 313 eligible SRs, including 86 for depression, 159 for type 2 diabetes mellitus, and 68 for chronic pain, very few (n = 29) had reported any sex effects. Most SRs that reported any sex effects used type of analysis called meta-regression, whereas 9 SRs used subgroup analysis or individual-patient data (IPD) meta-analysis (17).

Furthermore, in the study of Duan-Porter et al, the proportion of SRs that reported the sex distribution of primary studies varied from 31% (n = 8) for low back pain to 68% (n = 23) for trials about fibromyalgia. Primary RCTs also seldom reported sex effects, and most did not have an adequate sample size to examine them. The authors concluded that all SRs should

report the proportion of women enrolled in primary studies as well as evaluate sex effects using relevant methods whenever power is adequate (17).

Comparing this insufficient attention to sex-based analyses, previous studies have also described similar lack of attention to race/ethnicity in trials. A study of Geller et al. indicated that 21% of analyzed trials did not report race or ethnicity in their sample of participants, and 64% did not report any analyses based on race/ethnicity (12). Likewise, multiple studies reported that race/ethnicity was associated with important differences between participants when it comes to pain (19-21). For this reason, race/ethnicity should be reported among the baseline characteristics of patients and, when feasible, outcomes should also be reported based on race/ethnicity so that we can gain more insight into potential differences in the effect of interventions related to race/ethnicity.

In our study, 5 trials indicated in the Methods that they planned any race/ethnicity-based analyses, and 8 reported such results in the Results, excluding those that reported number of participants of different race/ethnicity. Less than ten percent of trials reported race/ethnicity of participants, and in those studies 74% of participants were described as white or Caucasian.

One of the reasons contributing to insufficient participation of non-white participants in clinical trials could be their unwillingness to engage in such activities. In a recent study, Pariera et al. explored willingness of people to participate in clinical trials by ethnicity. It was shown that indeed that there is a difference between ethnical groups in this respect. African-Americans and Hispanic-Americans had more negative attitudes towards clinical trials than white/non-Hispanics. The factors that affected the willingness were questions about who profited from the clinical trial. White and non-Hispanics expressed higher willingness to participate in a clinical trial if the trial would extend their life. African-Americans and Hispanic-Americans indicated they were more likely to participate if the doctor would profit from the drugs being tested. Interestingly, white/ non-Hispanics were most interested if the pharmaceutical companies would take an advantage out of that trial (24).

6. CONCLUSIONS

Based on the study results, we can conclude the following:

1. None of the analyzed trials stratified participants based on sex and race/ethnicity,
2. Proportion of included women and men was similar; on average percent of included women was 49% and 51% for men,
3. Less than 10% of analyzed trial reported information about participants' ethnicity,
4. Sex-related results were reported in 7.9% and race/ethnicity-related results were reported in 0.15% of analyzed trials,
5. Of the 52 trials that reported sex-related results, 20 (38%) described that there was a significant difference between women and men in at least one analyzed outcome; among 8 trials that reported results based on race/ethnicity, 1 (12.5%) trial reported significant difference in at least one analyzed outcome for participants of different race/ethnicity
6. Less than 5% of analyzed trials addressed sex/gender or race/ethnicity in Discussion.

7. REFERENCES

1. IASP International Association for the Study of Pain. Seattle: IASP Task Force on Taxonomy; 1994. IASP Taxonomy; 2012 May 22 [cited 2017 June 26]

2. Woolf CJ. Review series introduction What is this thing called pain ? J Clin Invest. 2010;120(11):10–2.

3. Grichnik KP, Ferrante FM. The difference between acute and chronic pain. Mt Sinai J Med. 1991;58(3):217-20.

4. Lohman D, Schleifer R, Amon JJ, Everdingen MV den B, Rijke J De, Kessels A, et al. Access to pain treatment as a human right. BMC Med . 2010;8(1):8.

5. Brennan F, Carr DB, Cousins M. Pain management: A fundamental human right. Anesth Analg. 2007;105(1):205–21.

6. Masic I, Miokovic M, Muhamedagic B. Evidence Based Medicine - New Approaches and Challenges. Acta Inform Medica [Internet]. 2008;16(4):219. Available from: http://www.scopemed.org/fulltextpdf.php?mno=6371

7. Burns P, Rohrich R, Chong K. The Levels of Evidence and their role in Evidence-Based Medicine. Plast Reconstr Surg. 2011;128(1):305–10.

8. Bilić-Zulle L, Đogaš Z, Grčević D, et al. Principles of Research in Medicine. Zagreb: Medicinska Naklada; 2008. p.35-49.

9. Stang A. Randomized controlled trials-an indispensible part of clinical research. Dtsch Ärzteblatt Int [Internet]. 2011;108(39):661–2.

10. Sibbald B, Roland M. Why are randomised controlled trials important? Bmj. 1998;316:201.

11. Kabisch M, Ruckes C, Seibert-Grafe M, Blettner M. Randomized Controlled Trials: Part 17 of a Series on Evaluation of Scientific Publications. Dtsch Arztebl Int. 2011;108(39):663-8.

12. Geller SE, Koch A, Pellettieri B, Carnes M. in Clinical Trials : Have We Made Progress ? J women's Heal. 2011;20(3):315–20.

13. Avery E, Clark J. Sex-related reporting in randomised controlled trials in medical journals. Lancet. Elsevier Ltd; 2016;388(10062):2839–40.

14. Racine M, Tousignant-Laflamme Y, Kloda L, Dion D,Dupuis G, Choiniere M, A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men? Pain. 2012;153:602-18.

15. Racine M, Tousignant-Laflamme Y, Kloda L, Dion D,Dupuis G, Choiniere M. A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? Pain. 2012;153:619-35.

16. Boerner KE, Eccleston C, Chambers CT, Keogh E. Sex differences in the efficacy of psychological therapies for the management of chronic and recurrent pain in children and adolescents. Pain [Internet]. 2016;8536(4):1. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006396-900000000-99359

17. Duan-Porter W, Goldstein K, McDuffie J, Hughes J, Clowse M, Klap R, et al. Reporting of Sex Effects by Systematic Reviews on Interventions for Depression, Diabetes, and Chronic Pain. Ann Intern Med. 2016;165:184–93.

18. Wiesenfeld-Hallin Z. Sex differences in pain perception. Gend Med. 2005;(3):137–45.

19. Martinez K, Snyder C, Malin J, I Dy. Is race/ethnicity related to the presence or severity of pain in colorectal and lung cancer? J Pain Symptom Manag. 2014;(48):1050–9.

20. Aseltine RH, Yan J, Gruss CB, Wagner C, Katz M. Connecticut hospital readmissions related to chest pain and heart failure: Differences by race, ethnicity, and payer. Conn Med. 2015;79(2):69–76.

21. Maher A, Leigh W, Brick M, Young S, Millar J, Walker C, et al. Gender, ethnicity and smoking affect pain and function in patients with rotator cuff tears. ANZ J Surg. 2017;

22. Kim AM, Tingen CM, Woodruff TK. Sex bias in trials and treatment must end. Nature. 2010;465(7299):688–9.

23. Welch V, Doull M, Yoganathan M, Juli J, Boscoe M, Coen SE, reporting of sex and gender in randomized controlled trials in Canada: a crosssectional methods study. Res Integr Peer Rev. 2017;1:2-15.

24. Pariera K, Murphy S, Meng J, McLaughlin M, Exploring Willingness to Participate in Clinical Trials by Ethnicity, J Racial Ethn Health Disparities. 2017 4;763-769

8. SUMMARY

Aim: The aim of this study was to assess reporting of data on sex and race/ethnicity in randomized controlled trials (RCTs) of interventions published in the highest-ranking journals from the field of anesthesiology.

Methods: We analyzed RCTs published from 2014 to mid-2017 in the seven journals belonging to the top 25% in the field of Anesthesiology according to the 2016 Journal Impact Factor published by the database Journal Citation Reports. We extracted data regarding terminology for sex/gender, proportion of participants according to the race/gender and race/ethnicity, and results shown for the race/gender and race/ethnicity.

Results: Among the analyzed 657 trials, none stratified participants based on sex/gender or race/ethnicity. Proportion of included women and men was very similar. Most of the included participants were white/Caucasian. Less than 10% of analyzed trial reported information about participants' ethnicity. Sex-related results were reported in 7.9% and race/ethnicity-related results were reported in 0.15% of analyzed trials. Of the 52 trials that reported sex-related results, 20 (38%) described that there was a significant difference between women and men in at least one analyzed outcome; among 8 trials that reported results based on race/ethnicity, 1 (12.5%) trial reported significant difference in at least one analyzed outcome for participants of different race/ethnicity. Less than 5% of analyzed trials addressed sex/gender or race/ethnicity in Discussion.

Conclusion: Sex-specific and race/ethnicity aspects are neglected in anesthesiology trials, even though on average these trials included similar number of women and men. Outcomes related to anesthesiology and pain may differ in participants related to sex and race/ethnicity. Therefore, trialists in the field of anesthesiology should invest more effort to plan, conduct and report sex--specific and race/ethnicity results. Predominant inclusion of white participants in anesthesiology trials should be reconsidered.

9. CROATIAN SUMMARY

Naslov istraživanja: Izvještavanje o spolu i rasi/etnicitetu u randomiziranim kontroliranim pokusima objavljenim u najboljim časopisima iz područja anesteziologije

Cilj: Istražiti načine izvještavanja podatka o spolu i rasi/etnicitetu u randomiziranim kontroliranim pokusima objavljenim u najboljim časopisima iz područja anesteziologije.

Metode: Analizirani su randomizirani kontrolirani pokusi objavljeni od 2014. do sredine 2017. godine u sedam časopisa koji se nalaze u 25% najboljih časopisa prema čimbeniku odjeka iz 2016. Godine koji objavljuje baza Journal Citation Reports. Izvađeni su podatci izvještava o analizima nja podataka o spolu i rasi/etnicitetu.

Rezultati: Analizirano je 657 pokusa. Niti jedan nije stratificirao ispitanike po spolu ili rasi/etnicitetu. Udio uključenih žena i muškaraca u prosjeku je bi podjednak. Većina uključenih ispitanika bili su bijelci. Manje od 10% uključenih radova opisalo je informacije o rasi/etnicitetu uključenih ispitanika. Rezultati koji se tiču analiza prema spolu objavljeni su u 7,9%, a rezultati analiza ovisnih o rasi/etnicitetu u 0,15% uključenih pokusa. Među 52 pokusa koja su prikazala podatke ovisno o spolu, 20 (38%) je opisalo značajne razlike u barem jednom ishodu ovisno o spolu, a u 1 (12,5%) od 8 radova koji su prikazali analize ovisno o rasi/etnicitetu prikazane su razlike prema tom aspektu. Manje od 5% analiziranih pokusa spomenulo je spol ili rasu/etnicitet u Diskusiji.

Zaključak: Klinički pokusi iz najboljih anesteziooloških časopisa zanemaruj aspekte spola i rase/etniciteta. Rezultati se mogu razlikovati ovisno o tome kojeg je spola i rase/etniciteta ispitanik pa je nužno u budućim istraživanjima planirati, provesti i opisati takve rezultate. Također je nužno uložiti više truda u uključivanje osoba različite rase/etniciteta u kliničke pokuse.

10. CURRICULUM VITAE

Personal Information

Name: Clemens Janda-Martinac

Date & place of birth: 28.07.1991, Essen in Germany

Citizenship: German

Address: Lakronstraße 54, 40625 Düsseldorf

e-mail: Clemijama@gmail.com

Education

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

2002 – 2011: Marie- Curie Gymnasium (secondary school) Düsseldorf

1998 – 2002: EGS Benderstraße Primary school Düsseldorf

Other Activities

August 2011 – September 2011: Work at a ward at Lionsgate Hospital Vancouver

March 2011: Nursery internship in St. Vinzenz Krankenhaus Düsseldorf

September 2010: Internship at St. Vinzenz Krankenhaus Düsseldorf