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Meta-analysis of Inline Filtration Effects on Post-infusion Phlebitis Caused by Particulate Contamination of Intravenous Administration

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ABSTRACT – The particulate contamination of intravenously administered fluid has been of major concern. One of the most common complications associated with long term i.v. therapy is post-infusion phlebitis (PIP). We undertook a systematic review and meta-analysis of the effect of inline filters on PIP. An electronic search of Medline, KoreaMed, and KRIST was conducted to identify randomized controlled trials evaluating the effect of inline filters. Meta-analysis was undertaken using STATA 10. A total of 62 literatures were retrieved, of which 7 were included in meta-analysis. Inline filtration for intravenous infusion significantly reduced by 39% of the incidence of phlebitis, with a relative risk of 0.61 (95% CI 0.41-0.90, p=0.012). Therefore, inline filtration is a highly effective means of decreasing the incidence of infusion phlebitis and should be considered as a part of intravenous therapy.

Key words – inline filter, phlebitis, intravenous infusion, meta-analysis

Unlike other medicinal preparations, the injection drug products are directly administered into the blood vessel. Therefore, the manufacture, quality control, and administration after opening of sterile injection products require more stringent control measures. However, the potential contamination of glass particles or other kinds of particulates during administration of the injection drug product in the glass container has been of major concern. Such particulates may, when accumulated in the body, damage the lung, kidney, liver, and other organs(Brewer and Dunning, 1947; Donaldson and Tran, 2002; Garvan and Gunner, 1964; LEHR et al., 2002; Lye and Hwang, 2003; Oberdorster et al., 2005). Especially, when intravenously administered, they may cause the phlebitis.

At present, however, there is no direct evidence showing the hazardousness of glass particles possibly introduced in the course of opening glass ampoules in human body. Further, clinical studies to investigate such effects of glass particles have not been conducted due to ethical considerations.

Instead, several clinical trials have been conducted with the use of inline filters for intravenous administration, and indirectly estimated the potential effects of glass particles and other particulate matters in human body. For those studies one of the most common complications associated with long term i.v. therapy is post-infusion phlebitis (PIP). When the incidence rates of phlebitis were compared among randomized clinical trials, mixed conclusions were observed and definite conclusions could not be drawn from individual trials.

Therefore the primary purpose of this study is to investigate the potential effects of particulate matters possibly introduced during intravenous administration through comparison of groups with and without use of inline filters. For the purpose firstly, published literatures relating to clinical studies on use of such filters were collected by systematic review. The systematic review of published literatures is widely recognized as a highly important approach to obtain supportive evidences. In other words medical literatures reporting the efficacy and safety in human body after removal of microparticles with use of the inline filter for intravenous administration were reviewed in order to evaluate the effects of glass particles and other particulate in human body.

Secondly meta-analysis was carried out to comprehensively review the existing data and provide more definite results.

Methods

PubMed(http://pubmed.gov), Cochrane Library(http://thecochranelibrary.com) and Google Scholar (scholar.google.com/advanced_scholar_search?hl=en&lr=), the internationally well-known search engines, were used to select published literatures investigating the adverse effects of particulate matters on human body with use of inline filters. In addition, KoreaMed(http://www.koreamed.org), KRIST and a search

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program at the National Assembly Library(http://www.nanet.go.kr) were also used to select appropriate literatures. However, with the difficulty in identifying relevant articles through electronic searching, an update search was conducted in the form of a citation search run on all of the relevant papers previously identified(June 2009).

Our search strategy included keywords to encompass: (i) specific characteristics of inline filter using device-based terms like 'inline filter' and 'inline filtration', (ii) specific types of literature such as Randomized Controlled Trials(RCTs) and systematic reviews and (iii) specific disease such as 'phlebitis'. A search strategy was developed for this purpose and the selection/exclusion criteria and quality criteria were applied to search results to finally select the most appropriate literatures. The "randomization" is an important factor for selection of literatures. Since several factors, in addition to particulate matters arising from injection containers, contribute to phlebitis, only the randomized, well-controlled trials were selected for this meta-analysis.

As described above, published literatures relating to the randomized, well-controlled trials in human subjects were selected for this meta-analysis. No limitation was applied to the types of subject groups for those trials. However, only trials relating to intravenous administration and potential introduction of glass particles or other particulate matters were selected. In addition, published literatures describing the safety and efficacy evaluation in light of phlebitis and written in English or Korean were included in this meta-analysis.

Literature search was carried out in three steps. First, predetermined key words were used to search literatures and duplicated search results were excluded. Second, the titles and abstracts were reviewed to select literatures meeting the pre-established selection criteria. Third, full texts of individual literatures were obtained and evaluated against the pre-established criteria to select the final literatures for meta-analysis through quality evaluation.

Further, in order to evaluate the methodological quality of individual literatures, the Jadad scale was employed(Jadad et al., 1996). Two investigators independently evaluated the methodological quality of literatures according to the Jadad scale and any inconsistencies were resolved through discussion and agreement. Authors and other important data on literatures were blinded in order to minimize bias. The agreement between investigators was expressed as the Kappa value. The Jadad scale consists of 5 items for 3 categories (randomization, double blinding, and withdrawals/drop-out). Each item was scored as follows: -1 (limited to "randomization" and "blinding"), 0, and 1 (total: 5 scores). When total score was not less than 3, the literature was evaluated as "high quality." If the randomization and double-blinding procedures were explained, one point was assigned to each category. In addition, one point was additionally given when the described procedures were found to be appropriate. On the contrary, one point was subtracted when the described procedures were inappropriate. After quality assessment, literatures were comprehensively assessed for their adequacy.

In this study, meta-analysis was carried out to investigate the effects of use of inline filters on the incidence of phlebitis. Clinical endpoint was the number of phlebitis cases from selected literatures. Since it was a categorical data, the percentage of subjects showing phlebitis in total subjects was used to calculate the relative risk. In addition, individual literatures were chronologically organized for cumulative meta-analysis. The aggregated effect size was calculated according to the inverse variance weighted method and the homogeneity was also tested during calculation. Since the homogeneity hypothesis was rejected ($p<0.1$), the random effect model was employed for analysis.

The funnel plots (x-axis: selected literatures, y-axis: the number of patients) were drawn and visually evaluated for any publication bias that may occur during meta-analysis. Then, the Begg and Mazumdar's ranking correlation and Egger's linear regression methods were used for statistical testing.

STATA/SE 10.0(StataCorp LP, College station, Texas, USA, http://www.stata.com) for Windows was used for all statistical analysis in this study.

Results

Identification and Characteristics of Studies

Pre-defined keywords were used to search literatures. Total 62 literatures were collected and 10 literatures were finally selected through quality assessment (step 3). 3 literatures concerning clinical trials in neonates and children were excluded(Foster et al., 2006; Lingen et al., 2004). Finally, 7 literatures were selected for this study (Figure 1). Further, since one literature contained two kinds of research results, total 8 clinical trials in 7 literatures were included in meta-analysis (Table I)(Adams et al., 1986; Allcutt et al., 1983; Bivins et al., 1979; Falchuk et al., 1985; Maddox et al.; Roberts et al., 1994; Rusho and Bair, 1979)

Such selected clinical trials were conducted between 1979 and 1994. No clinical trial in adults was found after 1994. 6 clinical trials among total 8 trials were carried out in patients before or after surgical operations. For the remaining two trials, patients receiving intravenous administration of antibiotics

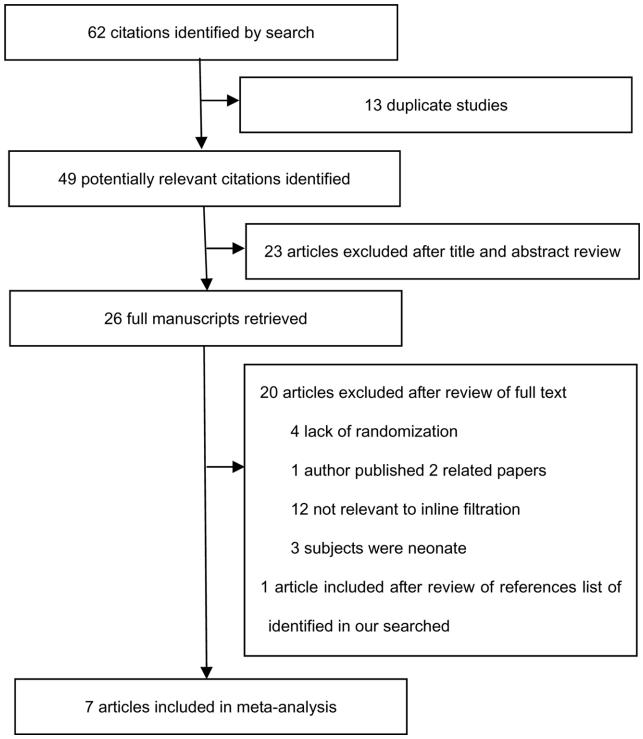

Figure 1. Flow chart of study selection.

and patients receiving intravenous administration for more than 48 hours were enrolled. In general, patients requiring intravenous administration for more than 48 hours were selected as subjects for clinical trials. The number of subjects was 40~264.

At present, hospitals in Korea use two types of inline filters: 1.2 mm lipid filter and 0.2 mm non-lipid filter. Depending on the capacity of endotoxin removal, the non-lipid inline filters are classified into two types: for replacement within 96 hours and for replacement within 24 hours. 0.45 mm filter not used in Korea was used in two clinical trials. Other clinical trials used 0.22 mm inline filters for replacement within 96 hours and with the capacity of endotoxin removal. All trials employed the control group for which filters were not used.

Risk of bias in included studies

Evaluation of 8 clinical trials for publication bias revealed that no publication bias was observed in the Begg & Mazumdar rank correlation test (p=0.386) and the Egger's linear regression test (p=0.696). In addition, apparent publication bias was not found in the funnel plots (Figure 2).

Methodological quality of total 8 clinical trials was evaluated according to the Jadad scale. 2 literatures were scored as "4 points", 3 literatures "3 points", and 3 literatures "not more than 2 points". Cohen's kappa value was 0.83, indicating relatively high agreement (p=0.0018). Allocation concealment showed the lowest score in all clinical trials. Allocation concealment was not mentioned in 7 clinical trials.

Effects of Inline Filtration on Post-infusion Phlebitis

In the randomized clinical trials, the incidence rate of phlebitis was 26~60% in the control groups for which inline filters were not used, while the incidence rate was 6~40% in the test groups for which inline filters were used. Although the test groups showed the relatively low values, statistical significance was not agreed between clinical trials. For meta-analysis, data from clinical trials were summarized and organized in tables and graphs. Although methods and conditions were slightly different between clinical trials, it was assumed that sufficient homogeneity was obtained for treatment methods and endpoints of those clinical trials.

In the meta-analysis, when exact number of subjects was not provided in the literature, total number of subjects was allocated into each group and the resultant percentage values were used for calculation of effective group and non-effective group. Since the selected literatures did not have completely agreed conditions and subject groups, the random effect model was adopted for the meta-analysis. Since it was a categorical data, the relative risk was calculated in this analysis. The relative risk was 0.61 (95% CI 0.41-0.90) in the meta-analysis, indicating that the relative risk for the group with use of inline filters was 0.61 times lower than that of the group without use of inline filters. This means that use of inline filters resulted in 0.61 times lower incidence rate of phlebitis, compared to the group without use of inline filters. In other words, it means that the incidence rate of phlebitis was reduced by 39%. This result was similar to the incidence rates in groups with and without use of inline filters. Weighting was applied to calculation and meta-analysis results are summarized in Figure 3. Further, review of cumulative relative risks from 1979 to 1994 revealed that the relative risk was 0.21 in 1979 (p value = 0.011) and statistically significant difference in the incidence of phlebitis was found between test groups (with use of inline filters) and control groups (without use of filters). The relative risk had been cumulatively increased and the relative risk was finally 0.61 in 1994 (p value = 0.012). It was confirmed that the confidence interval had been narrowed and the final value was statistically significant (Figure 4).

Discussion and Conclusion

Systematic review showed that the incidence rate of phlebitis was 50~70% in the long-term intravenous administration.

Table I. *Characteristics of Included Studies*

Reference	Year	Population .	No.of participants	Therapy
Rucho *et al.*	1979	Orthopedic surgery patients who were to undergo hip, knee, ankle or elbow replacements	150	Filter group: received infusions through 0.45 μm membrane filter Control group: no filter
Bivins *et al.*	1979	Orthopedic surgery patients	40	Filter group: received infusions 0.22 μm, no heparin, no steroid Control group: placebo
Bivins *et al.*	1979	General surgery patients	56	Filter group: received infusions 0.45 μm, set left in place 72 hours, non buffered solutions Control group: placebo
Allcutt *et al.*	1983	Patients with peripheral infusion of likely duration greater than 48h	194	Filter group: received infusions 0.2 μm inline filter Control group: dummy(a straight plastic tube)
Maddox *et al.*	1983	Patients(men) undergoing elective surgery	195	Filter group: received infusions 0.2 μm inline final filtration devices Control group: received therapy identical placebo devices
Falchuk *et al.*	1985	Patents on the general surgical services, who required intravenous therapy	264	Filter group: received infusions through 0.22 μm IVEX-HP filter cartridges Control group: received infusions through 18 to 20 gauge catheters
Adams *et al.*	1986	Patients received intravenous therapy via a peripheral vein on surgical units	102	Filter group: received infusions through 0.22 μm inline final filtration device Control group: received infusions through placebo devices
Roberts *et al.*	1994	Patients with cystic fibrosis receiving intermittent iv antibiotics	228	Filter group: received iv antibiotics through an 0.22 μm inline filter Control group: received iv antibiotics in combination with an infusate containing heparin 500 units and hydrocortisone 10 mg/L

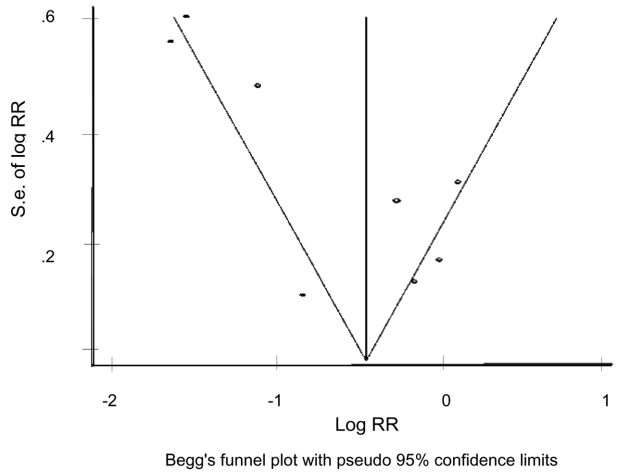

Figure 2. Funnel plot for publication bias.

Also the incidence rate of phlebitis was found to be reduced by using in-line filter.

In the meta-analysis, the relative risk value for the difference in incidence rate of phlebitis was 0.61 when inline filters were used, meaning that the incidence of phlebitis was reduced by 39% when compared to the group for which inline filters were not used. Since the confidence interval did not include 1, statistically significant difference was also demonstrated (p=0.012). Even though published literatures showed different results relating to demonstration of statistical significance, such heterogeneity was not significant and different clinical trials were evaluated as having sufficient homogeneity. Accordingly, it was concluded that the meta-analysis was reliable and justifiable.

The endpoint used in clinical studies on evaluation of safety and efficacy of inline filters in adults was the incidence of phlebitis in the test group, compared to that in the control group for which inline filters were not used. Phlebitis is a complication frequently occurred in connection with intravenous infusion and caused by many factors, such as catheter, infusion set, nature of drug, pH level of drug solution, osmolarity and bacterial contamination. Since this study results are based on the randomized controlled studies, we can safely assume that various covariates were controlled by randomization.

The methodological quality was evaluated in the course of

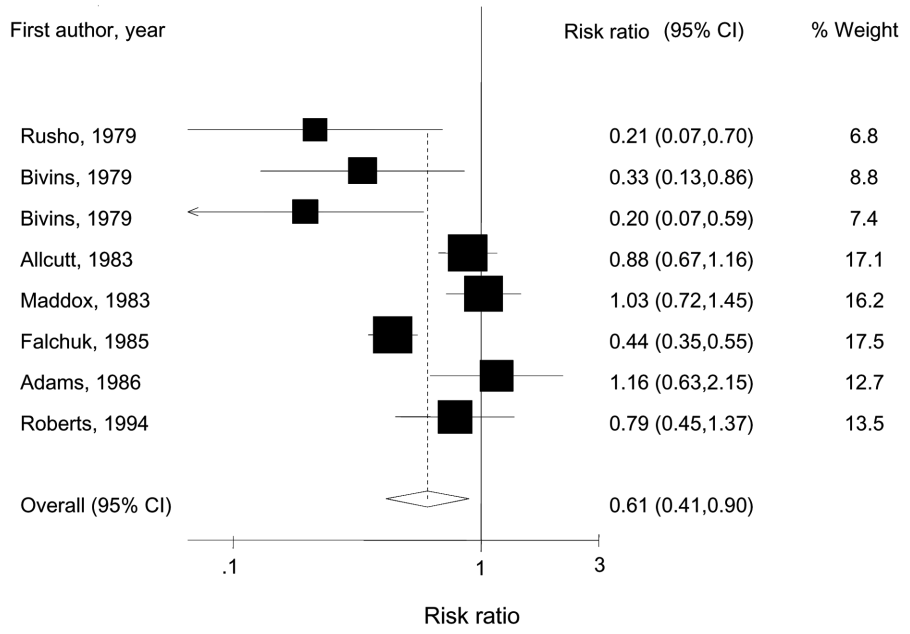

Figure 3. Meta analysis of phlebitis incidence in randomized controlled trial comparing inline filtration versus no filtration of intravenous infusion.

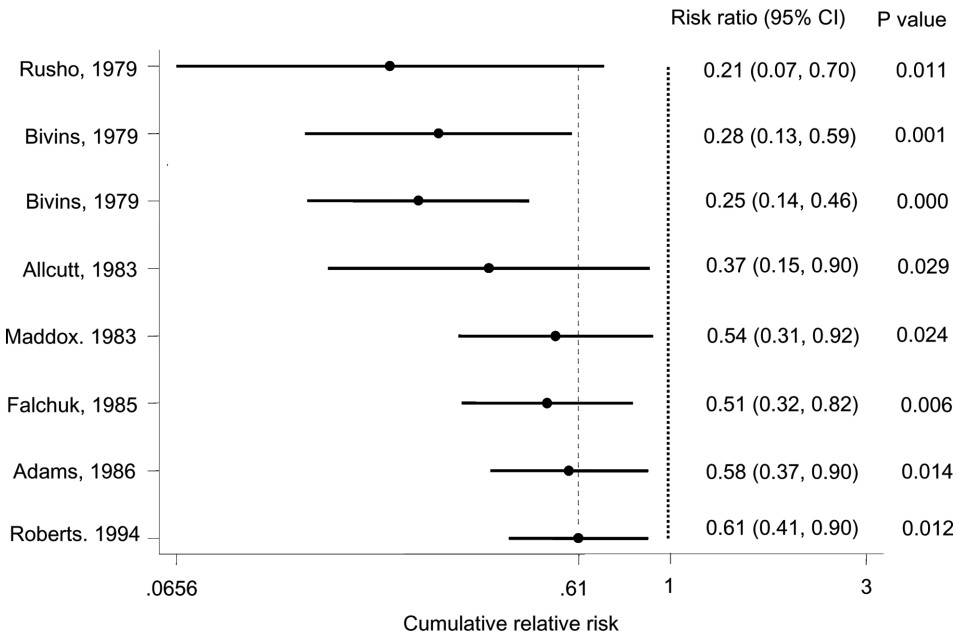

Figure 4. Cumulative meta analysis in chronological order.

selecting literatures for meta-analysis. However, since clinical trials were conducted between 1970's and 1990's, it was considered that they had some limitation, such as internal validity, in the design and conduct of clinical trials. There was limited number of studies with large-scale clinical trials meeting the modern requirements for randomized controlled trials.

Recently, the importance of evidence-based decision-making has been highlighted in the Korean health care sector. If a decision is made without sufficient evidence on safety, the patients' rights to get safe and effective treatment will be compromised and reasonable and efficient allocation of health care resources, such as national health insurance, will be interfered. Therefore, the decision-making process for health care policies has to be based on scientific and objective evidences. Further, such decision-making process has to be done in a transparent manner. One of the most important problems is that many decisions are

made on the basis of insufficient evidences. Thus more studies relating to adverse effects of injection containers have to be continuously collected to provide further supportive evidences.

Although many published literatures reporting the effects of inline filters showed potential hazardous effects of microparticles in human body, more comprehensive conclusions drawn from meta-analysis of these literatures will contribute to reasonable decision-making, protection of patients' rights and safer use of injection drug products. Especially the adverse effects of glass particles and particulate matters in human body are higher in patients receiving long-term intravenous administration, data from long-term intravenous administration into vulnerable patients are very helpful in providing clinical rationale for decision making. Further, it is expected that this study will contribute to safer use of injection drug products.

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Reference

Adams, S., Killien, M., Larson, E., 1986. In-line filtration and infusion phlebitis. J. Crit. Care 15, 134.

Allcutt, D., Lort, D., McCollum, C., 1983. Final inline filtration for intravenous infusions: a prospective hospital study. Brit. J. Surg 70, 111-113.

Bivins, B., Rapp, R., DeLuca, P., McKean, H., Griffen Jr, W., 1979. Final inline filtration: a means of decreasing the incidence of infusion phlebitis. Surgery 85, 388.

Brewer, J., Dunning, J., 1947. An in vitro and in vivo study of glass particles in ampules. J. Am Pharm. Assoc. 36, 289-293.

Donaldson, K., Tran, C., 2002. Inflammation caused by particles and fibers. Inhal. Toxicol 14, 5-27.

Falchuk, K., Peterson, L., McNeil, B., 1985. Microparticulate-induced phlebitis. Its prevention by in-line filtration. New. Engl. J. Med 312, 78.

Foster, J., Richards, R., Showell, M., 2006. Intravenous in-line filters for preventing morbidity and mortality in neonates. Cochrane. Db. Syst. Rev. 2.

Garvan, J., Gunner, B., 1964. The harmful effects of particles in intravenous fluids. J. Aust. Med. Assoc. 2, 1.

Jadad, A., Moore, R., Carroll, D., Jenkinson, C., Reynolds, D., Gavaghan, D., McQuay, H., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17, 1-12.

Lehr, H., Brunner, J., Rangoonwala, R., James Kirkpatrick, C., 2002. Particulate matter contamination of intravenous antibiotics aggravates loss of functional capillary density in postischemic striated muscle. Am. J. Resp. Crit. Care 165, 514.

Lingen, R., Baerts, W., Marquering, A., Ruijs, G., 2004. The use of in-line intravenous filters in sick newborn infants. Acta Paediatr. 93, 658-662.

Lye, S., Hwang, N., 2003. Glass particle contamination: is it here to stay? Anaesthesia 58, 93-94.

Maddox, R., John Jr, J., Brown, L., Smith, C., Effect of inline filtration on postinfusion phlebitis. Clin. Phamacy 2, 58.

Oberdorster, G., Maynard, A., Donaldson, K., Castranova, V., Fitzpatrick, J., Ausman, K., Carter, J., Karn, B., Kreyling, W., Lai, D., 2005. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Parti. Fibre. Toxico. 2, 8.

Roberts, G., Holmes, M., Staugas, R., Day, R., Finlay, C., Pitcher, A., 1994. Peripheral intravenous line survival and phlebitis prevention in patients receiving intravenous antibiotics: heparin/hydrocortisone versus in-line filters. Ann. Pharmacother. 28, 11.

Rusho, W., Bair, J., 1979. Effect of filtration on complications of postoperative intravenous therapy. Am. J. Health-Syst. Ph. 36, 1355.