# Meta Analysis of Series of Toxicities Assessment Trails of Various Preparations for Health Care based on Gastro Intestinal Disorders

**Most. Tajmary Mahfuz, Md. Mahmudul Hasan**

**Abstract**— The incidence of gastro intestinal disease is alarming problem all over the world particularly in third world countries like Bangladesh. Different tablet and liquid preparations are used to overcome the diseases. Different experiments are also conducted in different times on the different drugs of gastrointestinal diseases in the pharmacy lab. Among them some of the drugs are toxics. In a clinical trail the drugs are injected to the experimental animals and placebo are injected to the animals of the control group. All of drugs are measured on the basis of the results of the control group. The drugs are recommended on the basis of the results obtained from Meta analysis of series of trails. Meta analysis is the analysis of analyses which has combined the different results achieved from different analysis. Now a day, it has taken part in every important sector in our daily life by making pooled information through individual investigation. In this paper we have anticipated the side effects of different drugs used especially on gastro intestinal disorders through Meta analysis. Fixed effect model and random effect model have been used to draw inference regarding the side effects of the drugs by compared control group and experimental group. Meta analysis has been performed here to estimate the combined effect of toxicity. Moreover we have combined the effect size through forest plot which shows the results in graphical visualization.

**Keywords**—meta analysis; fixed effect model; random effect model; forest plot; control group; experimental group; clinical trial

## 1 INTRODUCTION

Meta analysis is the statistical procedure for combining data from multiple studies. To analysis the results from individual's studies, the statistical breakdown of a large collection called Meta analysis. Integrating the findings named Meta analysis which connotes a precise substitute to the casual, narrative discussions of research studies that symbolize our attempts to make sagacity of the rapidly expanding research literature.

To generalize the findings than any single study, this method has great precision. Moreover, as the most of the individual randomized trails in clinic research trails are too small, it increases power to arrive at a final conclusion for sub group analysis. The overall range of the effect size in any case of positive studies has shown by using Meta Analysis. Where several studies have shown inconsistence results with regard to magnitude or direction of an effect, Meta analysis is especially useful on that arena.

Meta-analysis of study of diagnostic tests, in particular, with many conflicting approaches for computing an overall estimate from the individual sensitivity or specificity values from these studies.

In this paper, we wanted to estimate to measure the series of toxicities assessment trails of various preparations for Gastro intestinal disorder by Meta analysis. Gastrointestinal disorders most commonly seen in the long-term cared population, including abdominal pain, gastro esophageal reflux disease (GERD), constipation, diarrhea, and gastrointestinal bleeding.

In this paper we have used two well known methods such as fixed effect method and random effect method of Meta analysis. In this paper, six studies(i.e. Ayurvedic preparations ) on different experiments on toxicity is of different Ayurvedic preparation used for treating gastro intestinal diseases have been considered. These experiments were conducted in Pharmacy lab of Jahangirnagar University [1].

To find out the side effect of those drugs, we have collected data from pharmacy lab of Jahangirnagar University and conducted toxicity assessment trails for diffident types of drug preparations on rats regularly. We have taken different measurement of each experimental unit on a regular basis and after a certain (59 to 62 days normally) period they sacrifice the rats and separate different organs (like kidney, lever, hearts, spleen etc) and measure the effect of toxicity level [2].


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## 2 LITRATURE REVIEW

### 2.1 Background

Planning a meta-analysis has significant to consider sources of variation in the studies that has being integrated in the meta-analysis. Variation with studies in effect magnitudes may arise from four sources: experimental, parametric, functional, and structural. When the procedures under studies have conducted lead to differences in effect sizes, the experimental variation arises. Parametric variation occurs when systems have governed by the same basic processes, yet differ in effect magnitudes generated by those processes. For functional variation, when systems have so distinct that the functions that described the interactions between variables assume different shapes and structural variation occurs when systems differ in their causal processes. One must be conscious of sources of deviation in effect sizes, in any event and through appropriate selection of an effect size measure or by conducting a mixed-model analysis, an explanation for such variant being given [3].

The method of merging study's results from separate but similar studies in order to generalize a conclusion regarding a particular research question, called Meta analysis has become one of the greatest growth area in medical research since 1980. [4]

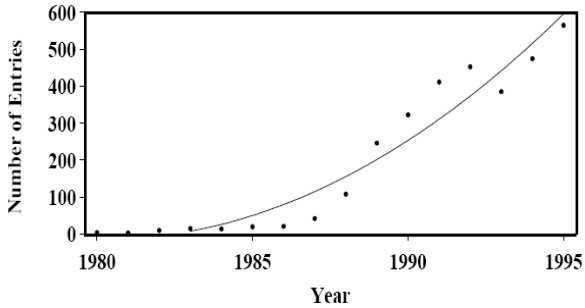


Figure 1: Using of meta-analysis over time in medicine

### 2.2 Related Work

This research work is actually extension of Elizabeth L C Merrall et.al [11], where they have shown some impact of drugs on prisons. Several researches have been done to find out the best practices of drugs. It has been always get privileges to test drug's impact on animals before human to provide best solutions for mankind.

## 3 META ANALYSES

Meta analysis is a quantitative procedure of joining the results of independent studies and synthesizing précising and winding up which may be used to appraise to create plan for new studies. Meta analysis is used here to check the data for its consistency, contamination, and version and to assess the basic characteristics of the data used in exploratory approach and to select the appropriate procedure as well as to modify an existence procedure to the study of gastro intestinal disorders. The method of statistically combining the findings of independent testing is known as meta-analysis, which is a quantitative re-evaluation of the outcomes of two or more studies. Meta-analysis is used by combining the results of several studies to accomplish an overall conclusion about the magnitude of a treatment effect, and can be executed whenever two or any other number of studies observes the same intangible hypothesis [5].

As Meta analysis is the mixture of outcome from multiple research studies [6], which involved by the following three steps-

1. Extract individual estimates and standard errors from each study,
2. Combine these estimates using a fixed or random effects model and
3. Testing for heterogeneity and graphically representation.

### 3.1 Basic Considerations of Meta analysis:

To estimate the side effect of the drugs used in gastrointestinal disorders through Meta analysis, some basic typical terms which related to conduct Meta analysis would discussed in this sub section [7].

**3.1.1 Odds Ratio:** Odds means an attribute can be defined as the result of dividing the proportion of individuals with an attribute by the proportion of individuals without the attribute in a population and the odds ratio (OR), contrasts the odds of exposure among cases with the odds of exposure among controls. Here OR considered as effect size and the toxicity's effect measure by compared among the expose and non expose group which have considered here experimental and control group [8].

**3.1.2 Relative risk:** The relative risk (RR) is a measure of association between a disease or condition and a factor under study [9]. The ratio of incidence in the exposed and non exposed is called relative risk (RR). In this paper we measured the side effect of the drugs by combined analysis where effect from different studies has combined and RR is also considered as another effect size.

## 4 RESULTS AND DISCUSSIONS

As we have discussed previous section that, our vision is to combined the different studies. In this paper we have combined the result found from different trials of gastrointestinal disorder applying different drugs used for gastrointestinal disorder on the experimental animals such as in different time periods. First we have identified the number of experimental units with toxicity. The toxicity is assed by comparing the experimental group with the control group. Then we have calculated the odds ratio and relative risk for every individual study and then we combined the odds ratios and relative risks by Meta analysis. For graphical visualization, we used an important tool called funal plot through which significantly visualized our findings [10].

Two well known methods such as fixed effect method and random effect method of Meta analysis have been described and applied to study for assessing the toxicity of the drugs used for the treatment of gastrointestinal diseases. From two

methods we have discussed that which model is appropriate by analysis Heterogeneity test. As early as we have discussed different experiments on toxicity of Ayurvedic preparations used for treating gastro intestinal diseases have been considered and effect sizes have been measured from OR and RR and finally their effect size combined by meta analysis. Results and discussions mentions below-

**Test of heterogeneity:**

To test the results, we have used the statistical software R. Testing of heterogeneity $I^2$, where I is a statistic that measures the proportion of inconsistency in individual studies. That cannot be explained by chance. Negative values are not allowed for $I^2$. If there is very little variation among the trials then $I^2$ will be low and the fixed effect model is appropriate [11].

$$I^2 = 0\% \ [0\%; 65.3\%]$$

Here the value of $I^2$ is 0% and 65.3% for the fixed and random effect model. As the values of $I^2$ is minimum between these two methods. We have chosen fixed effect method to get the optimum value of the research. The following table shows fixed effect method to draw Odds Ratio table.

| Drugs | Odds Ratio (OR) | 95%-CI (Confidence Interval) |
|---|---|---|
| knk (k=1) | 0.2143 | [0.0210; 2.1871] |
| rht (k=2) | 0.3857 | [0.1018; 1.4611] |
| asg (k=3) | 0.3114 | [0.1118; 0.8672] |
| ask (k=4) | 0.4722 | [0.2034; 1.0959] |
| brs (k=5) | 0.521 | [0.2468; 1.0998] |
| dsm (k=6) | 0.6165 | [0.3203; 1.1866] |

Table 1: **Cumulative meta-analysis for OR (Fixed effect model)**

The above table shows the odds ratio of every individual study, the confidence interval of the odds ratios.

Now, we have come with the point of combined analysis from the above figure has been drawn in forest plot.

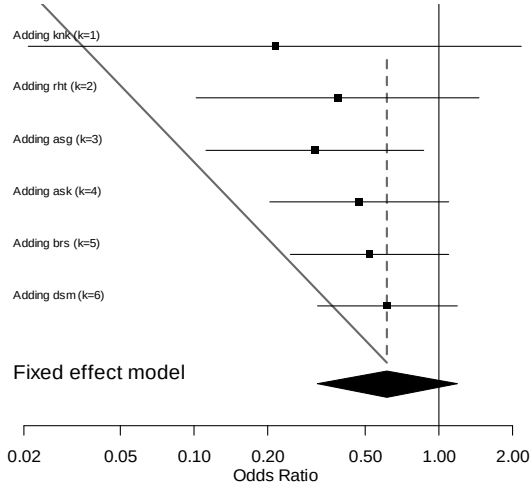


Figure 2: **Forest plot with the combined effect for OR**

From figure 2, the plot suggests that the Pooled estimate of the effect size from different studies is 0.6165. The confidence interval for the combined odds ratio is [0.3203; 1.1866]. The result indicates that the chance in favor of toxicity for the experimental group is (1/0.615) = 1.626 times than that of the control group [12].

The following table shows relative risks by using fixed effect model.

| Drugs | Relative Risk (RR) | 95%-CI (Confidence Interval) |
|---|---|---|
| knk (k=1) | 0.2667 | [0.0335; 2.1239] |
| rht (k=2) | 0.4818 | [0.1637; 1.4177] |
| asg (k=3) | 0.4196 | [0.1901; 0.9266] |
| ask (k=4) | 0.6581 | [0.3634; 1.1918] |
| brs (k=5) | 0.699 | [0.4229; 1.1554] |
| dsm (k=6) | 0.7654 | [0.4913; 1.1925] |

Table 2: **Cumulative meta-analysis for RR (Fixed effect model)**

The above table shows the odds ratio of every individual study, the confidence interval of the relative risk.

The forest plot for combined individuals studies of relative risks.

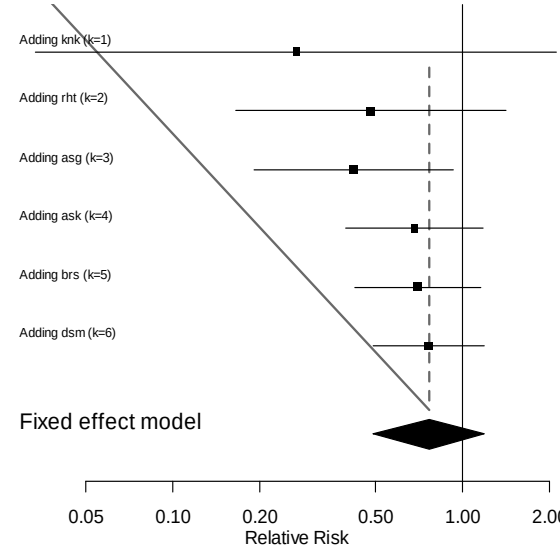


Figure 3: **Forest plot with the combined effect for RR**

By the fig 3, we have got the forest plot the combined effect size (relative risk) is designed by the relatively bigger box in the plot. The plot suggests that Pooled estimate 0.7654 and its confidence interval is [0.4913; 1.1925]. The plot is showing the combined effect relative risk with the diamond shaped box with all the individual relative risks from different studies. The combined relative risk is 0.7654.

## 5 WHAT WERE THE CHALLENGES?

As we have considered here the secondary data, it is being difficult to follow up the changes of those rats. So getting data was challenging in this aspects. To perform a Meta analysis for of series of toxicities assessment trails of various preparation, both fixed and random effect methods have been used. But to select the appropriate model we have faced some difficulties such as limitations of the fixed effect method to measure effects which are same for all trails. But it is not realistic to presume that the true individual treatment effects are identical. It seems sensible to believe that the treatment effects might vary to some extent. As Meta analysis has involved critical calculating procedures, we have faced critical challenges such as combining the individual's effect size.

## 6 CONCLUSION

In this paper, we have tried to find out the side effects of the different drugs used especially on gastrointestinal diseases by Meta analysis. The result indicates that the chance of the toxicity in the experimental group is more than that of the control group, which indicates the presence of side effects in the drugs. So, based on the combined analysis results, existence of toxicity has originated in the drugs.

There are many procedures of combining the results of the different studies in Meta analysis. This research work will help to decide the suitable model to analyze data. Moreover, this research work could help the analysis of human drugs by prior experiments and researches.

## REFERENCES


[1] Huque MF, "*Experiences with meta-analysis in NDA submissions. Proceedings of the Biopharmaceutical Section of the American Statistical Association*", 1988; 2: 28–33.

[2] *"Meta-Analysis Gaining Status in Science and Policymaking"* [1997] -Stephen P. Hoffert [Journal Article; from*The Scientist*, Vol. 11, n.18, p. 1, 5]

[3] Sacks H, Chalmers TC, Smith HJ, and "*Randomized versus historical controls for clinical trials."*Am J Med 1982; 72: 233–40.

[4] The Cochrane Controlled Trials Register. In: Cochrane Library. CD ROM and online. Cochrane Collaboration (issue 1). Oxford: Update Software, 2010.

[5] MM Hasan, Most Tajmary Mahfuz, Woakil Uddin Ahamed, Syed Akhter Hossain, " *Requirement Analysis for Context-Awareness to Create a Digital Persona in eHealth based Pervasive Intelligence Environment*", Journal of Information and Communication Technologies (ISSN 2047-3168), vol. 2, issue 3, pp.11-15, United Kingdom, 2012.

[6] Moher D, Jadad AR, Nichol G, Penman M,Tugwell P, Walsh S.A ssessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists.Controlled Clinical Trials 1995;16: 62–73.

[7] Chatellier G, Zapletal E, Lemaitre D, Menard J,Degoulet P. The number needed to treat: a clinically useful nomogram in its proper context.BMJ 1996; 312: 426–9.

[8] Last accessed on 10/04/2012 at 18:40 pm *www.intl.elsevierhealth.com/journals/ijmi]*

[9] Götzsche PC, Podenphant J, Olesen M, HalbergP, *"Meta-analysis of second-line antirheumatic drugs: sample size bias and uncertain benefit.J Clin Epidemiol"*, 1992; 45: 587–94.

[10] Bailar JC, Mosteller FFreiman JA, Chalmers TC,Smith H, Kuebl er RR ,"*The importance of beta, the type II error, and sample size in the design and interpretation of the randomized controlled trial"* In:Bailar JC, Mosteller F, eds. Medical uses of statistics. Boston, MA: NEJM Books, 1992:357.

[11] Elizabeth L C Merrall, Azar Kariminia, Ingrid A Binswanger, Michael S Hobbs, Michael Farrell, John Marsden,Sharon J Hutchinson, and Sheila M Bird, " **Meta-analysis of drug-related deaths soon after release from prison" ,** Society for the Study of Addiction, UK,2010.

[12] Bird SM, Hutchinson SJ. Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996–99. *Addiction*. 2003; 98:185–90.



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