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Meta-Analysis: A Convenient Tool for the Choice of Nose-to-Brain Nanocarriers

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Abstract

In terms of delivery to the brain, the intranasal route is a highly promising route. Nevertheless, it is one of the most challenging and complicated routes. As a outcome, researchers are constantly looking for novel drug delivery vehicles like polymeric and lipid nanoparticles that are likely to improve the bioavailability of the drugs that are given to the brain.A certain number of publications from various databases and the literature were selected for this study.In order to investigate the published studies and demonstrate the superiority of nanocarriers in increasing the bioavailability of various drugs in the brain, meta-analyses employing two distinct algorithms (DerSimonian–Laird and inverse variance) were carried out.In addition, lipid nanosystems and polymeric nanosystems were quantitatively compared. After normalization, the meta-analysis used the important pharmacokinetic parameter known as the area under the curve (AUC) from in vivo animal studies as the "effect."Plots of forest were created. Closure and key findings:After comparing it to more conventional preparations like solutions and suspensions, the meta-analysis found that the AUC increased.Most importantly, it was demonstrated that lipid nanoparticles were significantly superior to polymeric counterparts.

Keywords: Nasal; Nanocarriers; Polymeric; Lipid; Systematic; Meta-Analysis

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Introduction

The nose-to-brain drug delivery has been tried by a number of drug delivery researchers and manufacturers due to its numerous advantages.The ease of administration, non-invasiveness, proximity to the brain, and numerous other advantages, including overcoming one of the most difficult barriers for drugs to penetrate,the blood–brain barrier in addition to the avoidance of the first-pass effect (liver metabolism).are among the most significant advantages of this administration method. In particular, the last two benefits Outcomes in a significant increase in the drug's brain bioavailability in comparison to other conventional routes of drug administration like the oral and intravenous routes **[1-4]**.

Numerous attempts have been made to improve drug absorption and permeability through the blood–brain barrier and nasal mucosa.Drug nanocarriers and permeation enhancers are two examples of these attempts.A very effective method for delivering the drug molecule to the brain via the nose can be provided by the appropriate selection of the nanoparticulate materials **[5]**.Several hydrophobic or amphiphilic nanosystems, such as solid lipid nanoparticles, nanostructured lipid carriers, lipid nanocapsules, liposomes, microemulsions, PLGA, Pullulan and chitosan polymeric nanoparticles, and gelatin as protein nanocarriers, must be used to exploit the trigeminal and olfactory nerves for nose-to-brain delivery.

In addition, due to its significant benefits in the treatment of serious diseases, the controlled delivery of drugs is currently a subject of high significance at the industrial and academic levels. Compared to conventional systems and formulations, lipid-based nanosystems were found to be more effective at increasing oral drug bioavailability in a previous and recent meta-analysis study. Despite their distinct nature and chemical structure, polymeric nanoparticles have recently been shown to significantly increase the bioavailability of the aforementioned drugs **[6-7]**.Both types of carriers have advantages and disadvantages when it comes to nose-to-brain delivery.The highest advantage of the lipid vehicles is their high affinity for neurons and the blood–brain barrier (BBB).Contrarily, their polymeric counterparts are more robust, stable, and simple to modulate and conjugate. The goal

of systematic review is to answer a specific research question by gathering empirical evidence from predetermined eligibility criteria.Systematic review is considered a qualitative type of informatics tool by informatics researchers.Nevertheless, meta-analysis is regarded as a quantitative informatics synthesis tool that is associated with it.Meta-analysis is a cutting-edge statistical method for combining data from multiple studies and extracting it from multiple sources.It improves the precision and accuracy of the outcomes and Outcomes of the research studies **[8]**.In addition, it provides significant hypotheses and forecasts.After data normalization, meta-analysis is currently accepted as a very important method for analyzing and extracting important information from the available literature. In addition, in issues pertaining to healthcare that are based on evidence, meta-analyses play a crucial role.Case controls, case reports, cohort studies, and randomized controlled trials are all inferior to the meta-analysis method.Additionally, meta-analysis is acknowledged to be at the top of the evidence pyramid. There are numerous advantages to meta-analysis studies.Due to sample pooling, it increases statistical power.Additionally, the weight of the obtained closures is increased by this kind of analysis.Additionally, because it makes efficient use of the wealth of online databases and literature resources, meta-analysis is a practical and cost-effective type of analysis.Looking for the right information and precisely following the qualified standards are the main obstacles for this strategy **[9]**. The drug delivery field is currently incorporating the meta-analysis method.On the one hand, it is advantageous to compare novel formulations or advanced drug delivery systems to their conventional counterparts, and on the other, it is advantageous to compare multiple carriers and new delivery systems together.After that, it provides assistance in decision-making and introduces a brand-new tool for the pharmaceutical industry's choice of materials and carriers.

As a Outcomes, the pharmaceutics informatics tools of systematic review and meta-analysis were utilized in the current study.as an important indicator of the superior bioavailability of these advanced carriers to conventional formulations and to track the influence of delivering drugs using nanoparticulate systems on the area under the curve (AUC) **[10].**Another covariate was the type of nanoparticulate system used, such as lipids like liposomes, solid lipid nanoparticles, and lipid nanocapsules versus polymeric materials like chitosan, PLGA, Pullulan, and zein.

Methods

Inclusion Data and Criteria

The directed meta-investigation relied upon recording the region under the bend (AUC) as a fundamental pharmacokinetic boundary.Articles must meet a number of criteria in order to be considered for analysis, including being published within the last ten years (decade), coming from various locations, containing a variety of lipids and polymers, having a detailed methodology, demonstrating original data, and providing a comprehensive discussion of the loading of drugs in nanoparticulate systems used for nose-to-brain delivery.After evaluating the entire and full text, the entire collection of eligible articles was also thoroughly screened.Every one of the examined articles ought to introduce unique information and ought to have been distributed in writing data sets as examination articles.The area under the curve (AUC), or mean and standard deviation, of the pharmacokinetic parameter being investigated ought to be recorded in the articles. In each of the included studies, the control group's Outcomes with the investigated drug should be stated.The formulations in this group ought to contain the drug and be administered via nasal route in a conventional manner.The following is a list of the information that was gleaned from the articles that met the inclusion criteria:the drug's name, which was studied;the name of the author and the year the study was published;the number of animals used for both the conventional formulation group and the nanoparticulate system group;the kind of animal that is used;the kind of nanoparticulate system that is used (lipid versus polymeric);as well as the source of the material used to create the nanoparticulate system (natural versus synthetic).In order to compare the drug-loaded nanoparticulate systems with the control (the drug's conventional formulation), the AUC was used as a bioavailability indicator.The adopted meta-analysis's various parameters are depicted.

Meta-Analysis

A preliminary meta-analysis was conducted with the intention of confirming the bioavailability enhancement effect of loading intranasal drugs onto nanocarriers, as shown by the pharmacokinetic parameter, the area under the curve (AUC), which indicates the study's "effect."The Outcomes typically gathered from multiple sources are combined and projected in a comprehensive and conclusive manner in meta-analysis.As a direct Outcomes, the "heterogeneity" was also calculated was used to supply the two most important parameters:the study sample size, which is the number of animals used in the study, and the effect size, which is the AUC **[11]**.The forest plots, the distinguishing charts of this kind of statistical analysis, were provided after the Outcomes were meta-analyzed.

Due to the variability in the number of animals used in each study, the crucial and only permissible assumption of the fixed-effect model of meta-analysis that the only source of variation between studies should come from sampling errors was not met in the collected investigated studies of the current meta-analysis.As a Outcomes, the "DerSimonian–Laird method" and the alternative "continuous random-effects model" were used to calculate the overall effect size.

Another piece of software was used to verify the Outcomes further:Review Manager v.5.4.1 (Cochrane Collaboration, London, UK), which uses the inverse variance, a different algorithm, to calculate the overall effect size.In this analysis, the continuous random-effects model was also utilized. The various causes of variation among all studies are the focus of the random-effects model.The year of the study, the authors, the various drugs and their varying doses, the conditions of the various studies, the kind of animals used, the origin of the material used, the measurement method, and the sample size are all examples of these sources in the current study.As a Outcomes, and in a logical way, the random-effects model was deemed suitable for the meta-analysis that was carried out.Nevertheless, two significant statistical parameters were used to evaluate heterogeneity:the I2 index and Q statistic.The I2 index is regarded as an indicator

of the degree of heterogeneity, whereas the Q statistic provides an account of the presence or absence of heterogeneity among a study set that is related to all of the stated variables.The forest plot contained the calculated and presented 95% confidence interval (CI) for the standardized mean difference (SMD).The p-value was used to determine whether or not significance existed.The statistical approach known as leave-one-out meta-analysis was utilized in order to evaluate the study's robustness and sensitivity.

Result and Discussion

The pooled estimates of the SMD estimate were 9.2 and C.I. (6.5, 11.9) and 7.52 and C.I. (4.81, 10.23) for the OpenMetaAnalyst and Review Manager Outcomes, respectively, indicating that the overall SMD estimate was significant.The significance of the findings was confirmed by the fact that the upper and lower confidence intervals' values are greater than zero. The area under the curve (AUC), a crucial pharmacokinetic parameter, also demonstrates that the utilized nanocarriers have a real effect on the included drugs' bioavailability from the nose to the brain.

The leave-one-out meta-analysis, in which one study is ignored at a time and the analysis is repeated, was used to verify the findings.The pooled estimate for all of the performed and conducted analyses ranged from 8.3 to 10.3, demonstrating this method's high sensitivity and accuracy. Endocytotic or neuronal pathways are used by trigeminal or olfactory neurons to transport nanoparticles from the nose to the brain.Laser confocal scanning microscopy has previously demonstrated that the clathrin-coated pits can be followed by nanocarriers in the 20–200 nm range.On the other hand, caveolae-mediated endocytosis can be used to uptake larger nanoparticles between 200 and 1000 nm in size.Through endocytosis or pinocytosis, the nanoparticles can also be moved along the neuronal axon from the endothelial cells to the olfactory neurons.When the size of the nanoparticle falls within the range of 100–700 nm of the axon's diameter, this transport pathway takes place.Consequently, the intranasal delivery of nanoparticles is regarded as a promising platform for the treatment of life-threatening diseases like gliomas of various grades.In addition, when it comes to nanocarrier systems, the polymer-based nanoparticles and lipid-based nanoparticulate systems are the most promising nanoparticle classes that are the focus of brain-targeting research.

According to the two utilized software packages, the meta-analysis's heterogeneity score was relatively high, with an amount (Q) of 158.2 and quantitative degree of heterogeneity (I2) scores of 89% and 81%, respectively.This value was influenced by a variety of heterogeneous factors, including the variation in the year of the study, the number of used animals, the drug, the measurement types, the animal's climate and breeding conditions, and the various laboratories and researchers. The most significant factor in determining the weight of a study is the variation in the variety, number, and type of animals used, as well as the drugs and their dosages.As a Outcomes, an effort was made to improve the heterogeneity of the study.The studies that used odd weights, such asbeing less than 2% in weight were excluded.

The included studies were further analyzed in the literature and divided into two novel subgroups based on the kind of material used to synthesize the nanocarrier or nanoparticulate system: subgroup 1:the (a)-encoded polymeric nanoparticulate system;furthermore, subgroup 2:the (b)-encoded lipid nanoparticulate system.Using the two adopted software packages OpenMetaAnalyst and Review Manager, a subgroup meta-analysis was carried out in which the subgroup (a) pooled estimate score was 4.7 and 3.61 with C.I.s of (2.5, 6.9) and (1.59, 5.64), respectively;On the other hand, C.I.s (7.4, 19.6) and (6.40, 19.77) using the same software packages produced subgroup (b) pooled estimate scores of 13.5 and 13.08, respectively.The borders of the yellow or black diamond symbols generated by the two software packages depicting the two analyzed subgroups, in addition to the non-overlapping confidence intervals, indicate that there is a significant distinction between the two subgroups. The prevalence of lipid-based nanoparticulate frameworks in upgrading and expanding the bioavailability of their encased medications contrasted and the polymeric-based partners can be credited to the higher lipophilic properties of these transporters that surpass those of the polymeric contenders that lead to higher entrance capacity into the nasal mucosa and blood-cerebrum boundary, which, thusly, causes better bioavailability.Additionally, the higher lipophilicity increases the drug's affinity for the trigeminal and olfactory nerves, which are essential components of the delivery process from the nose to the brain.Because of this significant finding, the researchers would be motivated to focus on the kind of material used for drug delivery from the nose to the brain and, consequently, on the application of lipid nanoparticulate systems.These systems' high biocompatibility, safety, and toxicological profiles would be greatly enhanced by increasing their stability against oxidation and rancidity.

Conclusions

Nanoparticulate systems outperformed conventional formulations in terms of drug bioavailability via the nose-to-brain delivery administration route, as demonstrated by the meta-analysis study as a quantitative synthetic statistical tool.In addition, the overall standardized mean differences and their associated confidence intervals, as well as the forest plots generated by two distinct algorithm meta-analysis software packages, suggest that the meta-analysis performed in this study may be a useful tool for determining the best kind of carriers for this kind of delivery. The lipid-based nanoparticulate carrier systems performed better than their polymeric counterparts, making them the best nanocarriers.In the future, this study's Outcomes would encourage scientists and drug delivery researchers to increase their efforts to improve the stability of these important carriers, which is the main barrier to their widespread use in medicine despite their high bioaffinity, biocompatibility, and safety profiles.The main obstacle to the successful and advanced nose-to-brain drug delivery systems' development is still the stability issue.Nanoparticulate carriers that are driven synthetically and naturally did not differ significantly.This also means that scientists and formulators should focus on the choice of the materials for the carriers rather than their origins.

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Conflict of Interest

The author has no known conflicts of interested associated with this paper.

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