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3D PRINTING APPLICATIONS IN SURGERY: A REVIEW OF CLINICAL TRIALS AND ANIMAL STUDIES

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ABSTRACT

Purpose: In recent years, the use of 3D printing technologies in surgery has increased. We aimed to provide a perspective on the future of the use of this technology in surgery by compiling animal and clinical studies.

Methods: The clinical studies published in the "ClinicalTrials.gov", and the animal studies in "PubMed" were included in this review. We have included studies published until October 2019 in our review and conducted a statistical evaluation by classifying into categories, years, and countries.

Results: We evaluated the results of 70 clinical trials and 159 animal studies which were in compliance with our criteria. Animal studies were registered in 22 countries. 70 clinical trials were registered in 14 countries. A total of 4746 people were included in the clinical trials. In both animal studies and clinical trials most of the studies were performed in the field of orthopedics.

Conclusions: Our study has shown once again that 3D printing technologies are used in surgery-related branches. With the increasing number of research in the following years, we anticipate that this technology will become widespread in every field of medicine and will improve treatment protocols applied to patients.

Keywords: 3D printing , Surgery , Clinical trial, Animal study

CERRAHİDE 3B BASKI UYGULAMALARI: KLİNİK DENEY VE HAYVAN ÇALIŞMALARININ DERLENMESİ

ÖZET

Amaç: Son yıllarda 3D yazıcı teknolojlerinin tıbbın cerrahi branşlarında kullanımına yönelik çalışmalar artmıştır. Bu çalışmada da yapılmış hayvan çalışmaları ve klinik deneyler derlenerek bu teknolojinin gelecekteki kullanımına yönelik bir perspektif sunulması amaçlandı.

Metod: Ekim 2019'a kadar " ClinicalTrials.gov "da yayınlanan klinik deneyler ve " PubMed "de yayınlanan hayvan çalışmaları bu derlemeye dahil edilmiştir. Bu çalışmalar istatiksel olarak değerlendirilerek kategorilere,yıllara ve ülkelere göre sınıflandırılmıştır.

Sonuç: Bu kapsamda 70 adet klinik deney ve 159 adet hayvan çalışması değerlendirilmiştir. Klinik deneyler 14 ülkede , hayvan çalışmaları 22 ülkede gerçekleştirilmiştir. Klinik çalışmalara toplam 4746 hasta dahil edilmiştir. Hem hayvan çalışmalarında hem de klinik deneylerde en çok çalışma ortopedi alanında yapılmıştır.

Çıkarımlar: Yaptığımız çalışma bir kez daha göstermiştir ki, 3D yazıcı teknolojileri cerrahiyle alakalı tıbbi branşlar başta olmak üzere tıbbın birçok branşında kullanıma girmiştir. Gelecek yıllarda yapılan

çalışmaların artmasıyla birlikte bu teknolojinin tıbbın her branşında kullanımının yaygınlaşacağını bu sayede hastalara uygulanacak tedavi protokollerinin de geliştirileceğini ön görüyoruz.

Anahtar Kelimeler: 3B yazıcı , Cerrahi , Klinik deney , Hayvan çalışması

1. INTRODUCTION

3D printing technique builds structures based on a specific design and it is used to transform digital objects into physical models [1]. Creating 3D shapes over the last few decades has gained enormous speed and acceleration compared to the past by the invention of 3D printing (3DP) technology.

This technology or technique was firstly used for industrial prototyping such as jewelry and electrical components. It developed for use in a variety of fields in the progress of time [2] , [3]. The Medical field is one of the most developing and promising fields of this technology [4]. It facilitates most parts of daily medical practice such as education, preoperative planning, surgical care and patient-specific devices and treatments [6].

In addition, the advantages and disadvantages of 3DP technology in surgery are presented in the Table1.

Table 1: The reported advantages and disadvantages of 3D printing in surgery [7].

	Advantages	Disadvantages
1	Preoperative planning	Time-preparation
2	Accuracy	Additional cost per patient
3	Time-surgical procedure	Poor mechanical properties
4	Intraoperative guidance	Risks and complications
5	Better surgical results	Limited indications
6	Teaching and training	Results depended on the surgeon's skill and talent
7	Properties of the obtained object	Additional operating time
8	Feasibility	Supplementary equipment required (internal production)
9	Revision or reoperation	Lack of data for determining patient outcome
10	Library and replication possibilities	Low solidity
11	Helps to improve the skills and expertise of the surgeon	Low reproducibility of the impression material
12	Multidisciplinary approach	Too many stakeholders in the process

The 3D printing technique is useful in the preoperative planning of the complex anatomies. It allows the surgical team to select the appropriate implants or devices for the procedure. By simulating the surgical procedure, surgeons can also predict the possible difficulties [7].
Independent of the application, the use of 3D printing technology contributed to improving surgical patient safety by decreasing the morbidities. Many studies also reported a decrease in blood loss, and transfusion requirements [7]. The rate of discomfort was decreased, and better aesthetic/surgical results were obtained after surgery owing to the advantages and benefits of 3D printing technology with the use in surgical operations [7].

In addition, the 3DP technique provides a multidisciplinary environment that allows the cooperative work of different clinics to ensure good coordination.3D printing technology increases the cost of pre-operation but these personal anatomic models and personal special products decrease the cost of post-operation periods.

Cell culture application is followed by the experiment on animal models, and finally the sequence of human experiments in the research. This process is very important in terms of putting evidence and observing its applicability. It contributes to solving problems of living things and is a prerequisite for the studies on human beings. Therefore, conducting further animal studies have significant importance. Animal studies enable the development of 3D printing and many other areas for the purpose and transition stages. Various studies such as tissue production, prosthetic limb production, examination, and visualization of

chemical and physiological reactions in living things can be given as an example of animal studies in the field of three-dimensional printing. To the best of our knowledge, this is the first review of surgery-related 3D printing studies that includes clinical trials and animal studies.

2. MATERIAL AND METHOD

The clinical studies published in the "ClinicalTrials.gov" database and the animal studies published in " PubMed " were included in the review. The search was performed using the term: "3D printing". The articles – published until October 2019- that were related with surgery and animal study were included from PubMed. The studies in the field of veterinary medicine were included in our article considering that it would help the studies to be done in humans. Implant-related studies were not included in our article. The clinical trials that already started or completed before October 2019 were included from ClinicalTrials.gov.

3. RESULTS

We evaluated the results of 70 clinical trials and 159 animal studies which were in compliance with the criteria.

3.1. Worldwide distribution

Animal studies made with 3D printing technology were registered in 22 countries, and the USA was the first with 38 (23.89%) studies. China took second place with 36 (22.64%) studies and South Korea took third place with 30 (18.86%) studies. Other countries followed these countries with a various number of studies. (Fig 1).

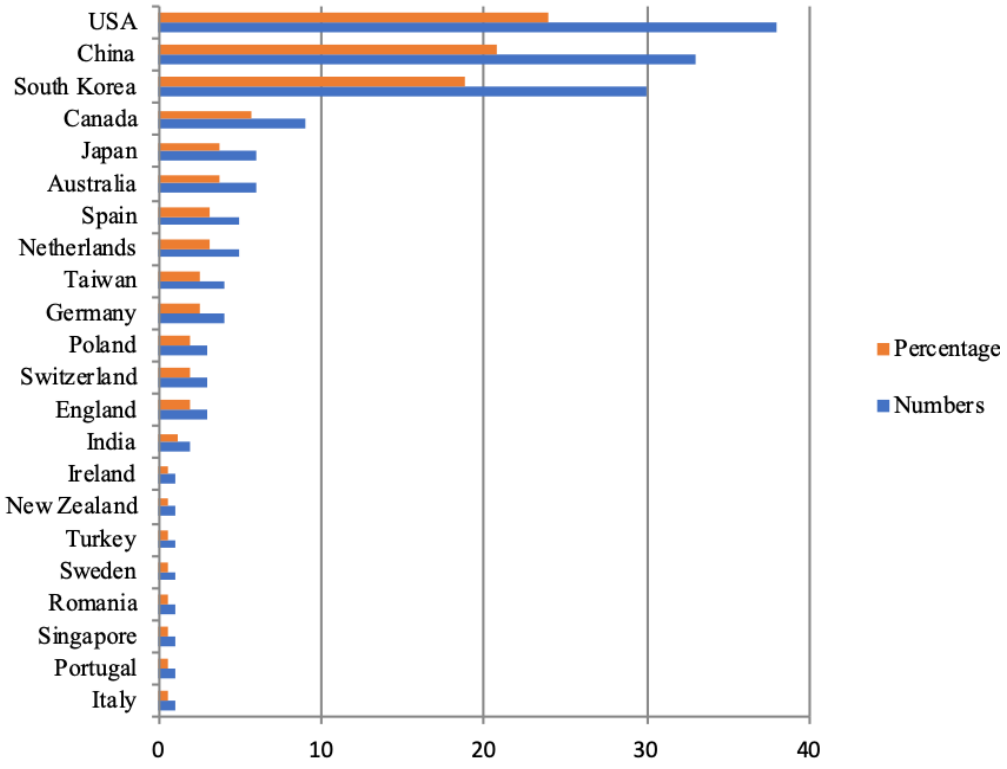

Figure 1. Distribution of animal studies by country

In clinical trials, 70 studies were registered in 14 countries. Most studies were conducted in China 26 (37.14%) and in the USA 17 (24.28%) . 27 trials were registered from the other 12 countries (Fig. 2).

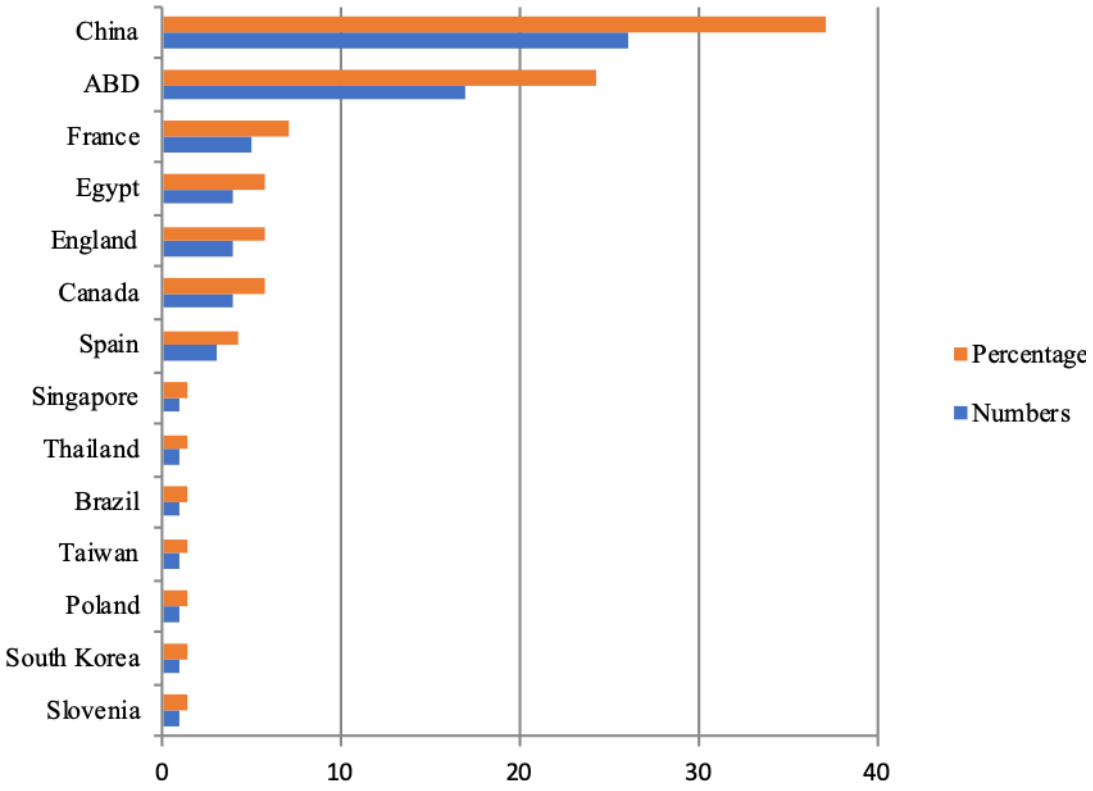

Figure 2. Distribution of the clinical trials by country

3.2. Distribution by years

Our research showed that the first study was published in 1998. Although a small number of studies were performed until 2014, there has been a huge increase in the number of studies since 2015. Twenty studies were found which was lower compared to the number of studies conducted in 2018 because our survey covered until October 2019 (Figure 3). The number of studies in 2019 is expected to exceed the number of studies conducted in 2018 by the end of the year. Our study showed that the number of articles in this field has increased significantly in the last 4 years. We anticipate that these studies will more accelerate in the coming years.

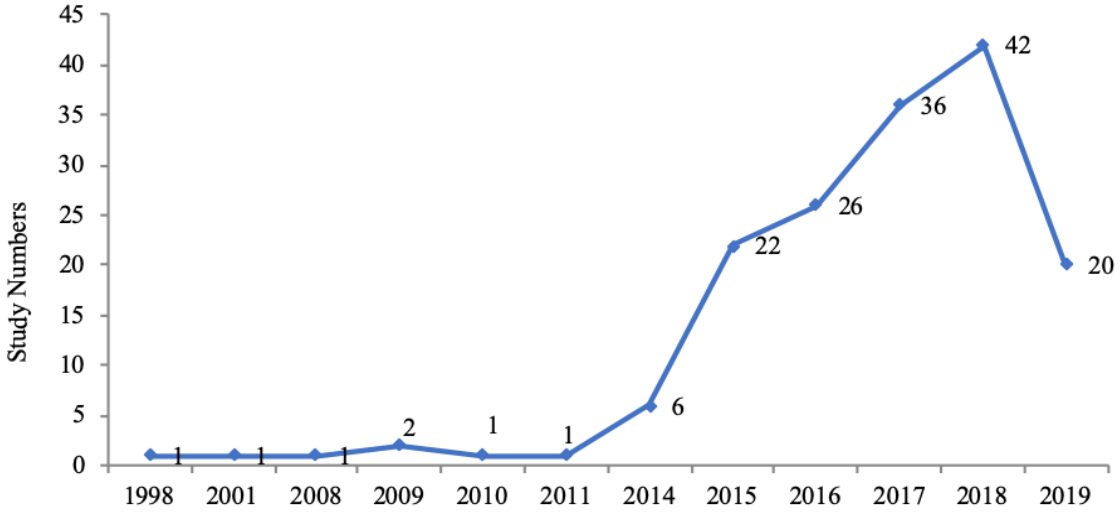

Figure 3. Distribution of animal studies by years

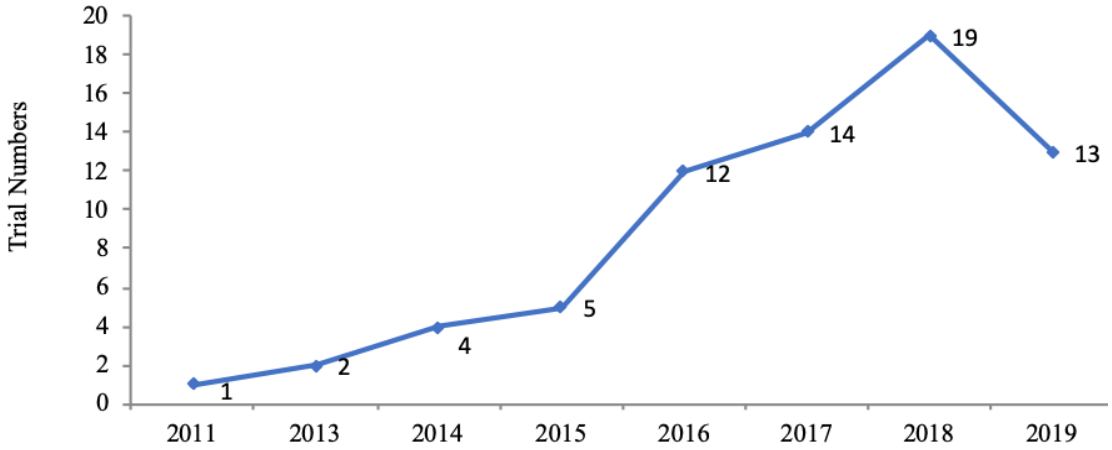

Figure 4. Distribution of clinical trials by years

In our research, we found that the first clinical trial was conducted in 2011. Considering the number of studies conducted in the first and second quarter of 2019, a large increase is expected in the number of studies by the end of the year compared to the previous years (Figure 4). This data shows that researchers become more and more interested in 3D printing technologies to improve our daily medical practice.

3.3. Classification by categories

Table 2. Classification of the animal model studies

Clinics	All results are n (n = 159)	
	Number	Percentage(%)
Orthopedics	**75**	**47,16%**
Oral and Maxillofacial Surgery	**25**	**15,72%**
ENT	**16**	**10,06%**
Cardiology	**11**	**6,91%**
General Surgery	**11**	**6,91%**
Pulmonology	**7**	**4,40%**
Neurology	**6**	**3,77%**
Urology	**3**	**1,88%**
Oncology	**2**	**1,25%**
Plastic Surgery	**2**	**1,25%**
Ophthalmology	**1**	**0,62%**

A total of 159 studies were divided into 11 categories. Orthopedics takes the first place with 75 studies and oral and maxillofacial surgery follows it with 25 studies. The remaining studies are divided into nine different categories. This table shows us that this technology is used in many different fields. We anticipate that such studies will be published in every branch of medicine in the following years (Table 2).

Table 3. Classification of the clinical trials

Clinics	All results are n (n = 70)	
	Number	Percentage(%)
Orthopedics	**21**	**30**
Pulmonology	**12**	**17,14**
General Surgery	**10**	**14,28**
Gastroenterelogy	**4**	**5,71**
Nephrology	**4**	**5,71**
Plastic Surgery	**3**	**4,28**
Oral and Maxillofacial Surgery	**2**	**2,85**
Neurology	**2**	**2,85**
Cardiology / CVS	**2**	**2,85**
Gynocology	**2**	**2,85**
Ophtalmology	**2**	**2,85**
Brain and Nerve Surgery	**2**	**2,85**
ENT	**2**	**2,85**
Dermatology	**1**	**1,42**
Radiology	**1**	**1,42**

A total of 70 clinical trials were divided into 15 categories. In clinical trials, as in animal studies, orthopedics takes first place with 21 studies. Pulmonology follows orthopedics with 12 studies. The remaining trials are divided into 13 different categories. As in animal studies, it has been demonstrated that clinical trials are conducted in various branches. We foresee that clinical trials related with 3D printing technologies will become widespread in every branch of medicine in the coming years (Table 3).

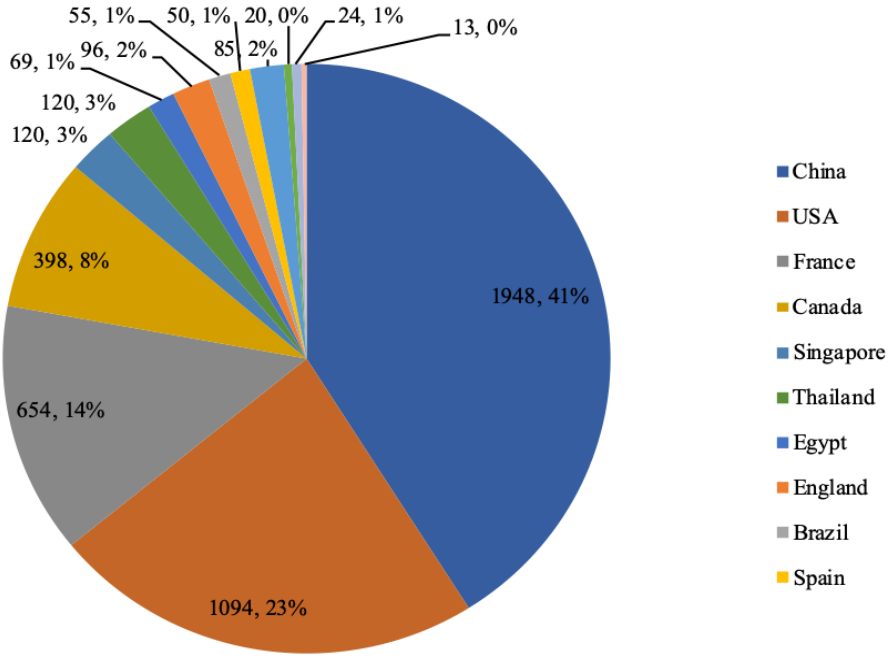

Figure 5. Patient distribution of the clinical trials by country (number; percentage)

A total of 4746 individuals were included in those clinical trials. The high numbers of participation are very important for evaluating the results of the trials. The statistics show that China is the leader with 1948 patients in 26 studies and the USA follows China with 1094 patients in 17 studies.

3.4. Examples from categories

3.4.1. Orthopedics

The studies in the field of orthopedics are mostly designed on 3D printed scaffolds on the correction of bone defects. In addition, there are also studies for the production of scaffolds where new bone tissues can be produced with the help of 3D printing.

3.4.2. Oral and Maxillofacial Surgery

The studies are based on the correction of anomalies of patients with head and facial bones (especially mandibular bone defects) via 3D printed models.

3.4.3. ENT

Studies have focused on producing artificial trachea produced by 3D printing in patients who need tracheal reconstruction (tracheal cancer).

3.4.4. Cardiology/CVS

There are studies on 3D printed vascular grafts. In addition, studies for the production of bioscaffolds in which decellularized ECM will be planted to ensure regeneration of myocardial tissue, which lost its function after a heart attack, are promising.

3.4.5. General Surgery & Gastroenterology & Nephrology

There are studies on 3D printed models that can simulate surgical interventions (renal surgery, liver surgery, pancreatic surgery) so that they can be used for pre-operative preparation and training for students.

3.4.6. Brain and Nerve Surgery

There are studies on 3D printed models that can be simulated for use in neurosurgery and surgical interventions (cerebral aneurysm) so that they can be used for pre-operative preparation and training for students.

3.4.7. Urology

There is a study on the production of 3D nano scaffolds to repair damaged bladder.

3.4.8. Oncology

There is a study on the production of 3D printed scaffolds for use in bone tumor therapy.

3.4.9. Pulmonology

Studies in this area aim to protect thoracic space and to produce artificial lung tissue in patients undergoing lobectomy using 3D printing technologies. Also, there are studies about evaluating the effectiveness and reliability of the localization of nodules.

3.4.10. Neurology

3D printing studies are used in the production of personalized masks in neurological diseases that cause facial deformities and the personalization of reminiscence therapies applied in dementia patients.

3.4.11. Plastic Surgery

3D printed materials are used to replace damaged bone and cartilage tissues, especially as a result of traumas and malignancies. Thus, it is aimed to protect the aesthetic image and body integrity.

3.4.12. Ophthalmology

The only study in the field of ophthalmology has been done to produce a trocar-cannula system for vitreoretinal surgery by using 3D printing technology.

3.4.13. Gynecology
3DP technology is used to design and manufacture applicators for the CT of the gynecological cancers.

3.4.14. Dermatology
By using 3D skin printings are aimed to reduce the anxiety of the patients before operation, to make them understand the operation process and to increase the patient's surgical treatment satisfaction.

3.4.15. Radiology
Body parts scanned with CT are printed in 3D and the printings are used as models for surgeries and training.

4. CONCLUSION
Our study has shown once again that 3D printing technologies are used in many fields of medicine especially surgery-related branches. With the increasing number of research in the following years, we anticipate that this technology will become widespread in every field of medicine and will improve treatment protocols applied to patients.

4.1. Future Projection
3D printing-related studies contain three important stages: animal experiments, human studies and human applications. When we look at the past, we saw that animal experiments and human studies were conducted successfully. In the near future, we will see human applications for treatment in medicine.

We foresee two main potential treatment way that we can use 3D printing technology:

Supposing that there is an organ that begins to lose its function in the body and advances towards failure. We will transfer the scaffold to the appropriate location in the patient's body. Then we will plant appropriate stem cells on this scaffold. In time, this organ will develop in the body. When the organ that is present in the body loses its function, we remove that organ and place the organ that we produce in the appropriate place in the patient's body.

Secondly, let's assume that a part of an organ in the body is damaged. During the operation, the coordinates of this damaged area will be determined by imaging technologies to be developed. Then the appropriate stem cells to be taken from the body will be purified and transplanted with the help of robotic arms and treatment will be provided.

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