Does The Prophylactic Administration Of Pre-Hospital Antibiotics Reduce Infections In Adult Patients With Open Limb Fractures?

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Contents

1. Introduction

Open fractures are characterized as a condition when a fragment of bone perforates the skin and becomes indirect with the external environment, usually as a consequence of high-energy traumatic injury (Zalavras et al., 2008). Open fractures of the limbs, especially the lower extremity, are grave orthopedic injuries that pose a high risk of infection and non-union (Atwan et al., 2020). Treatment of such injuries requires compliance to Advanced Trauma Life Support guidelines, which mandates the administration of antibiotics soon after sterilizing the wound. As an initial treatment of open fracture of extremities, almost all the high-income countries resort to using antibiotics who perceive that their benefits outweigh their potential risks. In the USA, the "Joint Committee for Accreditation of Healthcare Organizations (JCAHO)" requires 100% compliance to this requirement for hospital re-credentialing. However, in various low income countries, antibiotics use is restricted for various reasons such as lack of awareness, cost, failure to recognize the case by healthcare staff, availability, or reliance on traditional healthcare. In few scenarios, the use of antibiotics for open fractures is detained until the patient visits the secondary or sometimes the tertiary care centers. However, given the fact that open fracture is characterized as a contaminated wound, it is mostly perceived that the administration of antibiotics is therapeutic, rather than prophylactic and it prevents the occurrence of subsequent infections such as recurrent abscesses and infected non-unions (Gosselin et al., 2004). Gillespie (2001) stated in his review that prophylactic administration of antibiotics should be to the patients who undergo surgical treatment of closed bone or hip fractures (Gillespie and Walenkamp, 2010). Therefore, we have designed this study to remove the ambiguity related to

pre-hospital prophylactic use of antibiotics in open limb fractures and assess if such administration reduces the complaint of infection.

2. Literature Review

2.1 Selection Strategy

An online search was conducted with the assistance of a biomedical information specialist in the Embase database, PubMed, and the Web of Science. The electronic search was limited to studies of the 21st century. The prime search concept was the following: open limb fractures, pre-hospital antibiotic prophylaxis, and infection (secondary material). The final selection of the studies was made according to the following criteria (Whitehouse et al., 2017): 1) participants– patients with open limb fractures; 2) intervention –immediate, local or intravenous, delivery of antibiotics soon after the incidence of open fracture site; 3) clinical outcome – infection at the site of the fracture, evaluated till the specified follow-up period (Metsemakers et al., 2018) and 4) study design 5) comparator- prophylactic antibiotics. The criteria of study design selection were: retrospective and prospective observational study frameworks, and randomized controlled trials (RCTs) evaluating the efficacy of prophylactic antibiotics versus delayed or no antibiotic administration in open limb fractures**.** A total of 17 studies were assessed out of 6 excluded due to below mentioned reasons. The following table present the initial search strategy:

Database	Embase	PubMed	Web of Science
Dates searched	2000-2010	2011-2015	2016-2021
Open limb fracture	1	1	1
Infections in limbic fractures	2	1	
Antibiotic administration protocol in limbic fractures	1	2	
Prophylactic antibiotic administration	1	3	3

2.2 Excluded articles

The studies were excluded if any of the following characters was observed: research on pediatric patients or animal trials, administration of intravenous or local antibiotics for treating established infections; the fractures which were either a result of HIV infection or ulcers; open fractures at the site other limbs; open fractures which were caused as a consequence of military conflict,

gunshots or explosion; related articles from 19th century and lastly non- English studies were not considered. Based on this criteria articles authored by Bragha et al., Mangiaritti et al., Garin et al., Dellinger et al., Roddy et al., and Kefale et al. (Braga et al., 2013, Mangiarotti et al., 2000, Garin et al., 2006, Dellinger et al., 1988, Roddy et al., 2020, Kefale et al., 2020).

2.3 Included Articles

The study conducted by Gosselin et al., is included, their finding demonstrates the evident benefit of administrating antibiotics early as if it is administered within 3 hours of injury infection rate is 4.7 % On the other hand, the infection rate rises to 7.4 % if an antibiotic is given after three hours (Gosselin et al., 2004). However, there is a study including the analysis of 237 open leg fractures, which did not significantly reveal the effect of timing of antibiotic administration on the occurrence of infections (Al-Arabi et al., 2007). Initially, the location and Gustilo grade of fractures was not taken into account and all open fractures were grouped. Subsequently, 137 patients with open tibia fractures of Gustilo grade III were assessed by Lack et al. Their study demonstrated that delaying the administration of antibiotics for more than 66 minutes after injury and wound coverage for more than 5 days after injury cause deep infection (Lack et al., 2015). They strongly recommended the creation of a management plan that includes the administration of prophylactic antibiotics for reducing the chances of infection in open tibia fractures of high grade. Harper et al studies that there are many barriers in the timely administration of the antibiotic course. For instance, at their hospital, cefazolin was given within an hour but administration of gentamycin was delayed because of logistic issues like its unavailability in close proximity (Harper et al., 2018). Siebler et al demonstrated the importance of early antibiotic delivery as a part of prophylactic protocol. They stated that it effective to

administer antibiotics within one hour of injury; however, no clear guidance was provided regarding the route of antibiotic delivery (Siebler et al., 2020).

Although the effectiveness of systemic intravenous antibiotics has improved, yet local prophylactic antibiotics are also used successfully in various forms. As in complex open fractures, vascular anatomy is distorted so intravenously administrated drug has less concentration at the local site. If an antibiotic is injected directly into the site of injury, vascular deficiency can be overcome (ter Boo et al., 2015). Moreover, local antibiotics can help in the reduction of biofilm formation and bacterial colonization in internal fixation (Craig et al., 2014). The efficiency of vancomycin powder locally administrated on an open fracture site was assessed by the METRC group through a random control trial (O'Toole et al., 2017). They compared the occurrence of deep infection rate in 6 month period between those who received vancomycin and those who didn't. The population included ranged from 18 to 80 years having tibial plateau or pilon fractures and were treated by plate fixation. Upon comparison, those receiving vancomycin powder had an infection rate of 6.7% and others had 10.3 %. Moreover, the rate of gram positive bacteria was 3.7% in the vancomycin treated group and 7.8% in others (O'Toole et al., 2017). Although, the study assessed the role of early administration of antibiotics it was a secondary objective while the authors focused to differentiate between local and intravenous administration.

Moreover, a survey revealed that members of the Orthopaedic Trauma Association have a consensus that in case of open infection prophylactic antibiotics should be administered in less than 60 minutes. They studied 1106 patients and found out that early treatment with antibiotics has a major effect on reducing infection rate (Obremskey et al., 2014). In a review study, eight related studies were analyzed and the data from 1106 participants were evaluated. In the

quantitative analysis, it was found that prophylactic administration of antibiotics significantly diminished the occurrence of wound infection (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.29 to 0.65). As compared to controls (no antibiotics), who had a risk factor of 0.11 (53/461) of developing wound infection, the experimental group (received early antibiotics) had a risk factor of only 0.05 (33/645), thus witnessed a significant risk reduction of 0.07 (95% CI 0.03 to 0.10) (Craig et al., 2014). In 2003, Stevenson et al. conducted a placebo-controlled comparison of local administration of prophylactic flucloxacillin with placebo in 193 fracture cases. The results found out that 3% of patients among the antibiotic group developed an infection while the infection rate remained 4% in the placebo group. The difference was found to be statistically insignificant. Thus, it was concluded that prophylactic administration of antibiotics to local management of the wound is not effective in mitigating the risk of infections (Stevenson et al., 2003). Similarly, Singh et al found the immediate application of topical vancomycin as ineffective. However, the study is perceived to have a major risk of bias relatively small sample size, and insufficient analysis of soft-tissue involvement and follow-up period (Singh et al., 2015).

In a surprising study, Moehring et al observed the increased risk of fracture-related infection on administering loaded antibiotics- loaded carriers (8.3% vs 5.3%). However, a considerable risk of bias can be associated with the study as the authors fail to report patient prognostic factors, insufficient case-matching with Gustilo–Anderson grade, infection grading system, and no clear primary outcome was given. Moreover, it can be interpreted that a higher infection rate might be due to a smaller tested population and due to only single dose administration to the tested population while the control group was given delayed antibiotics for a longer duration (Moehring et al., 2000).

Lawing et al., in their study, raised the concerns regarding growing anti-microbial resistance and constructed the hypothesis if prophylactic use of antibiotics contributes to increasing the resistance. To test this, the authors designed an observational trial and evaluated the effect of immediate local administration of aqueous aminoglycosides in the open limb. The result rejected the hypothesis and found that prophylactic use of antibiotics decreased the infection rate significantly (9.5%) when compared with controls (19.7%). Moreover, no side effect of aminoglycosides was observed on bone union or its healing (Lawing et al., 2015).

The review of the literature revealed that even the use of antibiotics, especially local, is carrying out for decades, but studies on their beneficial effect are limited. Even some studies concluded the negative or no effect of antibiotics on reducing the risk of infection. Moreover, some studies also present a risk of bias due to their failure to include the criteria of the primary outcome of the treatment. Similarly, few studies mentioned any approved sample size calculation technique. The major limitation in the existing studies was the absence of the "pre-hospital" factor in their study. The present study is designed with an aim to fill the existing gaps in the literature and to test the efficacy of pre-hospital administration of antibiotics. The study will be a rational contribution in medical sciences and would possibly increase awareness regarding pre-hospital use of antibiotics.

3. Research Proposal

3.1 Methodology

3.1.1 Study design

Since the study aims to evaluate the effect of a specific clinical intervention (prophylactic administration of antibiotics), a mixed method approach can be used for the realization of the objective, where both qualitative and quantitative data is integrated for the synthesis of final

analysis (Pole, 2007, Moffatt et al., 2006). For the collection of qualitative and quantitative data, a retrospective review is proposed (Roddy et al., 2020, Harper et al., 2018). This will allows observation and comparison of the studied groups, control and experimental, till the specified follow-up period (Ranganathan and Aggarwal, 2018, Rezigalla, 2020). The qualitative data could be converted into quantitative data by interpreting according to a verified scale, for instance scaling of infection level as per Gustilo-Anderson classification (Kim and Leopold, 2012a). Moreover, the continuous quantitative variables can be directly evaluated which designates it descriptive research. On the other hand, the study could also adopt a non-blinded randomized control trial strategy (Panday et al., 2019). However, it has a higher risk bias (Mansournia et al., 2017). Similarly, it is not possible to blind the participants to the pre-hospital treatment, thus blinded-randomized study design is not possible for the current research. Therefore, the study will adopt the retrospective observational approach.

The study will regard prophylactic antibiotic administration as an independent variable whereas fracture-related infections (FRI) will be considered as a dependent variable (Panday et al., 2019). The efficacy of the intervention can be observed by comparing the experimental group with the control group whereas the placement of the subject in each group will be random, depending upon the data in the hospital registry (Cook, 2015, Reichardt, 2009).

3.1.2 Sample

Since it is an observational study at the core, the prospective patients were selected from a prospectively pooled orthopedic consultation database from the period last two years from 1st January 2019 to 1st January 2020. The data will be cross-checked by comparing medical record labels and date of birth with the prospectively collected data from the "general surgery trauma consult registry". The individual patient charts along with this registry will be utilized for the

abstraction of eligible patient's data and its validation. The selection of two study groups will be made through the non-probability purposive sampling technique (Vehovar et al., 2016). The following are the inclusion and exclusion criteria of the sample selection.

3.1.2.1 Inclusion Criteria

All the adult patients with age equal to or greater than 18 from all sexes, who visited the emergency department with the complaint of open limb fracture will be included in the study.

3.1.2.2 Exclusion Criteria

The patients with an age less than 18 years were excluded from the initial review. Moreover, the pregnant females and patients who reported allergic response to ceftriaxone or any other beta-lactam drug were not assessed for clinical data. Patients with no detailed documentation in the registry, who presented 24 hours after the injury or who could be followed for less than 1 month after the injury will be excluded from the study. Injuries out of the time bracket of the study will also be excluded.

3.1.2.3 Grouping Strategy

Following two study groups will be made after initial collection of the sample (patient's data in this case)

- Intervention group: Patients who visited the hospital through ambulance and were administered antibiotics, intravenously or locally, before reaching the hospital will be considered as an intervention group (Harper et al., 2018).
- Control group: Patients who received a dose of antibiotics 120 minutes after reaching the hospital (Werline and Young, 2020).

3.1.3 Data Collection Tool

The patients will be initially assessed for underlying comorbidities such as diabetes, alcoholism, smoking, obesity, psychiatric illness, blood pressure, use of heparin, cirrhosis, chronic renal disease, respiratory disease, and history of any skeletal accident (Marmor and Kerroumi, 2016). Injury-specific variables will include the type of open fracture, type of bones involved, the applicability of tourniquet, and injury severity score (ISS). Fractures will be classified into upper, including clavicle, humerus, radius, ulna, carpal, metacarpal, phalanges, and lower limb injuries which include the pelvis, fibula, tibia, tarsals, calcaneus, femur, metatarsals, phalanges, or femur (Ehrsson et al., 2000). The intraoperative findings, recorded at the first surgical debridement, will be used to classify open fracture type by using the Gustilo classification (Gustilo and Anderson, 1976, Kim and Leopold, 2012b). Hospital registry and patient's dispensation logs will be assessed for date of fracture, time of patient's contact with an ambulance, time of presentation of participants of the control group in the emergency department (ED), the period between presentation of participants in ambulance and ED to the first antibiotic administration, last follow-up date. To assess the prime outcome data related to surgical site infection (SSI) rate will be collected as recommended by "Center for Disease Control and Prevention in the National Healthcare Safety Network (NHSN) Patient Safety Component Manual" (Woldemicael et al., 2019). The criteria of SSI diagnosis of indoor patients include time taken for the coverage of soft tissue, length of stay in the hospital, length of stay in ICU (if ICU was attended), and reporting of sepsis in any case whereas outdoor patients will be assessed by their urge to visit the hospital with the complaint of fracture related infection (Henriksen et al., 2010). Time to the antibiotic will be calculated from the difference of time of ambulance or ED presentation and time of the first dose of antibiotic. The Follow-up time period was calculated by finding the

difference between the date of initial presentation and the date of discharge or last follow-up. The study will not include time to debridement as evaluation of previous studies demonstrated no signs of this variable on SSI, if the debridement is executed within a day (Pollak et al., 2010, Weber et al., 2014).

3.1.4 Data Analysis

An SPSS version 20.0 will be used for statistical analysis. Descriptive statistics will be computed for both continuous and categorical variables. For ease of interpretation, data will be tabulated in the form of mean, percentages, and median, where appropriate. Despite while analyzing the data both mean and median will be calculated, the existence of outliers might skew the computations with mean values. To avoid this, the median will be considered as a better representor of central tendency (Hubert and Van der Veeken, 2008). To evaluate the association of potential secondary variables on SSI, such as age, diabetes, blood pressure problems, sex, obesity, smoking, drug abuse, unbalanced alcohol intake, mental disorder, upper versus lower limb fractures, and Gustilo grading (Hendrickson et al., 2020, Penn-Barwell et al., 2012). Similarly, the bi-variable analysis will be performed to find out the time difference of antibiotic administration among participants within the group. For the comparison of categorical data between two study groups, a chi-square test will be used (McHugh, 2013). Whereas, Mann-Whitney U test will give a reliable comparison of continuous data (McKnight and Najab, 2010). The specific and sensitive threshold time to administration of antibiotics related to SSI will be assessed by receiver-operator specific analysis of the entire time between initial appearance and antibiotic administration. “A Cox proportional hazard model with multivariate regression” (Hsieh and Lavori, 2000) will be used for adjustment of effect of confounding variables such as smoking, drug abuse, and age on SSI. A P-value less than 0.05 will be considered statistically significant.

3.1.5 Reliability and Validity

The potential bias associated with non-probability sampling techniques will be removed by the inclusion of another researcher and statistician who will be informed of the criteria of study but will be kept blinded by the objectives of the research. This will mitigate the risk of selection bias (Penn-Barwell et al., 2012). As already mentioned, the univariate and multivariate analysis will be made to remove the effect of confounding variables on the validity and reliability of the results (Austin, 2011). The potential risk of human error while documenting the patient's data will be addressed by the incorporation of a data cross-checking strategy while collecting the data. For cross-checking, two separate records of the patients will be assessed. The participants in both the study group will be age and sex-matched to remove any inter-group differences based on these variables. Statistical analysis will also be reviewed by a well-trained statistician. Since all the patients with open limb fractures are considered in the study, it was ensured that patients of both the groups receive same drug line antibiotics. As the selection of patients with the different antibiotic courses can challenge the efficacy of antibiotics rather than their time of deliverance (Rodriguez et al., 2014). Lastly, the hospital staff and ambulance management team were kept blinded to the objectives of the study as their inferences might influence the researchers.

3.1.6 Ethics

Since the study doesn't involve direct research or investigation on human patients; therefore, "professional codes of conduct" are not applicable (Hussey, 1996). In case of any future clinical trials based on the results of this study, a former approval would require to be sought from the "ethical review board" or "ethical committee" of the institution (Greenwood, 2016, Association, 2001). However, the participants of the study will be informed of the identity of the researcher, the study's objective and expected methodology, and written consent will be taken after ensuring

them about the confidentiality of their data. To achieve this, all the selected patients will be contacted even through phone calls or email. The participants will also be given the liberty to withdraw from the research at any time during the study period (CADY, 2000, Kakar et al., 2014). The selection of the participants of the study will not be discriminated on the basis of their nationality, ethnicity, race, religious affiliation, and sex role, as guided by the Equality Act (2010) (Lockwood et al., 2012, Wadham, 2010). Moreover, according to "General data protection regulation" (2018), the data of the participants and the analyzed results will be stored in a systematic way where no external component can affect its credibility (Regulation, 2018).

3.1.7 Limitations

The major drawback in the proposed study is the inability to conduct randomized controlled clinical trials which are considered more effective in assessing the effect of interventions. Additionally, the sample/data collection is restricted to one institution only. It is likely that the ambulance staff of the assessed institution is trained while the scenario is different in other institutes. Complete reliance on hospital registry and non-inclusion of any witness is another gap in the study. The further narrowing of data on the basis of specific administered antibiotics would have enhanced the reliability of the results. The study excluded the individuals under the age of 18 which indicates the inapplicability of the study's result on those individuals.

3.2 Conclusion

Given the exposure of open limb fractures to the external environment, they are at high risk of developing deep infections. It is also likely that patient might develop life-threatening sepsis or the loses his infectious limb (Marecek et al., 2018). Therefore, the proposed study is a rational contribution to medical sciences. Despite the above mentioned limitations in the study, the study is perceived to play a significant role in limiting the growing concern of infectious diseases.

Moreover, the emergence of antibiotic resistance, which is assumed to be the next big cause of increased mortality in the coming decade, occurs mainly due to delayed, incomplete, or ineffective antibiotic treatment (Natan and Banin, 2017). The study has tried to address the 'delayed administration' causative factor of the resistance mechanism. Thus, addressing the challenge of antibiotic resistance as well. Based on the proposed methodology, the study will be conducted within ethical consideration. The results of the study will be discussed with the board of recognized national orthopedics and physicians for their critical analysis. Based on their analysis and recommendations, it is aimed to further the results with the national health department. It is expected that the government health officials will delineate a binding health policy to ensure the pre-hospital administration of the antibiotics if such administration is proved effective in limiting the infection.

Moreover, it is recommended to conduct further studies based on human clinical trials on a larger sample size. Participants from multiple institutions should be included and it should be aimed to specify the pre-hospital antibiotic administration time.

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