Research Article

Medical and Clinical Case Reports

Prevention of Surgical Site Infection in Neurosurgical Practice: A Review of Efficacy of Use 10% Povidone Iodine with or without 4% Chlorhexidine Solutions

Ashafa Isa Birnin-Gwari* and Aliyu Muhammad Koko

Department of Neurosurgery, Regional centre for Neurosurgery, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.

***Correspondence:**
Ashafa Isa Birnin-Gwari, Department of Neurosurgery, Regional Centre for Neurosurgery, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.

Received: 29 Dec 2022; **Accepted:** 26 Jan 2022; **Published:** 30 Jan 2022

Citation: Birnin-Gwari AI, Koko AM. Prevention of Surgical Site Infection in Neurosurgical Practice: A Review of Efficacy of Use 10% Povidone Iodine with or without 4% Chlorhexidine Solutions. Med Clin Case Rep. 2022; 2(1): 1-6.

ABSTRACT

***Background**: Surgical site infections following Neurosurgical procedures are often associated with significant morbidity and mortality; constitute added economic burden and affect the patient's quality of life negatively.*

The primary source of pathogenic microorganisms is the patient's skin flora, making preoperative skin antisepsis a primary focus for preventive strategies.

***Objective**: To review literature on various antiseptic agents used in neurosurgical practice and find out the most appropriate and effective agent(s) in preventing surgical site infections.*

***Methods:** A search in PubMed and Google scholar was made and various published articles on the use of antiseptic agents in preventing SSI in neurosurgery were reviewed.*
***Results:** Reviewed literature revealed that sequential use of 4% chlorhexidine and 10% povidone iodine is associated with significant reduction in both transient and resident's pathogens, as well as surgical site infections.*

***Conclusion**: A review of relevant scientific literature supports sequential use of 4% chlorhexidine and 10% povidone iodine in prevention of surgical site infections in neurosurgery.*

Keywords
Neurosurgery, Surgical site infection, Chlorhexidine, Povidone Iodine.

Introduction
"Antisepsis relieved patients from the terrors of death and gave to the surgeon restful nights and joyous days." William Williams Keen.

Surgical site infections refer to the infection of tissues, organs or spaces exposed by surgeon during invasive procedure occurring within 30days of the procedure or 1year if an implant is used [1]. They are common complication of surgical interventions and remain a burden on clinical practice.

Surgical site infections are the most common nosocomial infections responsible for approximately 20% of health care related infections and 40% of surgical infections in the United States [2,3].

The rate of surgical site infections in neurosurgery varies, ranging between 0.8- 8.1% worldwide [4-14].

Surgical site infections following Neurosurgical procedures are associated with devastating outcomes and high economic costs because of prolong hospital stays, additional investigations, requirement for complex treatments, in some cases re-operation. The long-term sequelae such as seizures, hemiparesis will hinder economic productivity, loss of wages and consequently compound the financial burden.

The development of surgical site infection occurs when bacterial contamination of the surgical site overwhelms the host's immune system. Skin commensals, such as Staphylococcus aureus, Coagulase negative staphylococci, Propionibacterium acne and, to a lesser extent, Acinetobacter baumannii, Enterococcus faecium, Klebsiella pneumonia, Pseudomonas aeruginosa are the most common pathogenic organisms implicated in Neurosurgical surgical site infections [5,15-21].

The primary source of pathogenic microorganisms is the patient's skin flora [5], making preoperative skin antisepsis a primary focus for preventive strategies.

Preoperative skin preparation of the surgical site using appropriate antiseptic products is one of the important interventions to prevent surgical site infections. The aim of surgical preparation of the skin with antiseptics is to remove transient microorganisms on the skin surface and to reduce the resident flora to a low level.

The idea that wounds can be rendered less prone to infection has been recognized since antiquity. Hippocrates described the use of wine (alcohol) to prevent infections in wounds during the 4th and 5th centuries before Christ [22].

The modern concept of preoperative skin preparation was birthed in 1867, when Joseph Lister, a British Professor of Surgery, used a carbolic acid aerosol to disinfect the skin before surgical incision and documented a significant reduction in postoperative morbidity and mortality [23]. Lister found a reduction in mortality from compound fracture wounds following application of Carbolic acid from 45% to 15% [24]. He later introduced the use of carbolic acid spray in the operating area.

Over the years, many substances were introduced as antiseptic agents including phenol, tincture of iodine, surgical spirit/ethanol/isopropanol, Merthiolate, hexachlorophene, quaternary ammonium compounds, iodophor, and chlorhexidine [22-24].

Classifications of surgical site infections

Horan and Colleagues proposed a classification system for surgical site infections according to the anatomical depth of the infections into Superficial incisional, Deep incisional and Organ/Space Surgical site infections, was adopted by Centre for Disease control and Prevention (CDC) [25].

Superficial incisional surgical site infection involves the skin and subcutaneous tissue, deep incisional involving the fascia or muscle layers, and organ/space involves an organ or a space.

Surgical site infections following Cranial procedures comprise a spectrum of infectious processes; superficial incisional scalp infections, deep incisional infections such as subgaleal abscess, calvarial osteomyelitis, cranial epidural abscess and organ/space infections such as, bacterial meningitis, ventriculitis, subdural empyema, and cerebral abscess.

Surgical site infection following spinal surgeries include: superficial Incisional involving the skin, and subcutaneous tissue, deep incisional involve the fascial and muscle layers, and Organ/space SSIs occurring below the fascial and muscle layers which include the following: osteomyelitis, diskitis, epidural spinal abscess, and per prosthetic joint infections.

Microbiology of Neurosurgical SSI

The etiological agents of surgical site infection following Neurosurgical procedures can be monomicrobial or polymicrobial. The resident polymicrobial flora comprising of aerobic and anaerobic bacteria, mainly the Staphylococcus aureus, Coagulase negative Staphylococci (Staph epidermidis), Propionibacterium acne, Acinetobacter baumannii and resident fungi are the main agents implicated in post Neurosurgical SSI [26].

The most common pathogen implicated is Staph. Aureus accounting for 40-50%, followed by Coagulase negative (Staphylococcus epidermidis) and Propionibacterium acne [5,15,18-20,27].
Other pathogens responsible for neurosurgical surgical site infections include Acinetobacter baumannii, Enterococcus faecum, Klebsiella pneumoniae, Pseudomonas aeruginosa among others [5,15,18,19,27,28].

Pathogenesis of Surgical Site Infections

SSI commonly occurs following invasion of the surgical wound by pathogens during surgical interventions leading to contamination. The most common source of this contamination is from the patient's endogenous skin flora. Other causes of infection include operating room personnel, hematogenous seeding, or early postoperative contamination.

This interplay between the host and pathogen is represented by the Altemeier equation [29].
Risk of SSI = Bacterial contamination X Virulence of the bacteria/Host resistance.

The first step in the pathogenesis of SSI is the contamination of the surgical site by the pathogens, and the dose of inoculums required is 10,000 colony forming unit per gram of tissue or per ml, though a lesser dose is required in the presence of foreign materials [30].

The degree of bacterial contamination depends on the class of the surgical wound. Berard and colleagues classified surgical wounds, which were adopted by Centre for Disease Control and prevention (CDC) into; Class I (clean), Class II (clean/contaminated), Class III (contaminated), and Class IV (dirty wounds).

Clean wounds **(class I):** These are surgically created wounds in which no inflammatory focus is encountered, no break in aseptic technique and no microbiologically colonized hollow viscus is entered.

Clean/contaminated wounds **(Class II):** include those in which a hollow viscus such as the respiratory, alimentary, or genitourinary

tracts with indigenous bacterial flora is opened under controlled circumstances without significant spillage of contents.

Contaminated wounds **(Class III):** include open accidental wounds encountered early after injury, those with gross spillage of viscus contents such as from the intestine, or incision through inflamed, albeit non-purulent tissue.

Dirty wounds **(Class IV):** include traumatic wounds in which a significant delay in treatment has occurred and in which necrotic tissue is present, those created in the presence of overt infection as evidenced by the presence of purulent material, and those created to access a perforated viscus accompanied by a high degree of contamination.

However, Narotam and colleagues classified neurosurgical wounds based on degree of contamination into 5 classes [31].

Clean

Surgery is usually elective, under strict aseptic conditions, with closed suction drainage placed in the subgaleal space for a period not exceeding 24 to 48 hours.

Clean with foreign body

"Clean with foreign body", cases would meet all other criteria for clean surgery but would have permanently or temporarily implanted foreign materials present, namely, shunts, intracranial pressure monitors, reservoirs, and ventricular drains. Large metallic foreign materials such as methyl methacrylate (acrylate) are included. Smaller metallic foreign materials such as aneurysm clips and ligaclips were excluded. Sutures (vicryl) and monofilamentous materials (stainless steel wire) used for standard neurosurgical procedures and routine wound closure were also excluded.

Clean contaminated

Known risk factors in the "clean contaminated" group were entry into the paranasal sinuses, cranial base fractures, breaches in standard surgical techniques, and surgery taking longer than 2 hours.

Contaminated

Although no frank sepsis was present, contamination of the operative site was known to have occurred, namely, compound skull fractures, open scalp lacerations at the operative site (older than 4 h), patients with CSF leakage, and finally, a subsequent operation at the same surgical incision within a period of 4 weeks.

Dirty

The "dirty" category comprised patients with sepsis already present at the time of surgery, namely: brain abscess, subdural empyema, ventriculitis, meningitis, osteitis, and purulent skin infection.

Virulence of the bacterial agent also contributes to the establishment of the deleterious effects on the host. Some bacteria produce enzymes that help to invade deeper tissues, also some damage could be aggravated by the production of toxins by the bacteria. Exotoxins are releases by viable bacteria, while endotoxins are integral cell wall component that are release only on microbial cell death.

Following contamination, the bacteria begins to grow and divide, however without provoking host response –a process called colonization.

The continued growth, multiplication and invasion of the host tissues leads to cellular injury and hence host response which could be local (Surgical site infections) or systemic, in severe cases.

CDC Criteria for Diagnosing SSI

Horan and colleagues devised a system of diagnosing and grading the severity of SSI, which was adopted by CDC. They classified SSI into three groups namely superficial incisional SSI, Deep incisional SSI and Organ/Space SSI-depending on the site and extent of the infection [25].

Superficial Incisional SSI is defined as the Presence of the Following Two Criteria;

1. Infection occurring within 30 days of procedure.
2. Involve only the skin or subcutaneous tissue around the incision.

At least one of the following criteria:

1. Purulent discharge from the superficial incision.
2. Organism isolated from an aseptically obtained culture of fluid or tissue from superficial incision.
3. At least one of the following signs or symptoms of infection; pain or tenderness, localized swelling, redness or heat and the superficial incision is deliberately opened by the surgeon unless the incision is culture negative.
4. Diagnosis of superficial incisional SSI made by a surgeon or attending physician.

Superficial incisional SSI is divided into two (2)

1. Superficial Incisional Primary (SIP): Superficial incisional SSI in the primary incision in a patient who has had an operation with more than 1 incisions.
2. Superficial Incisional Secondary (SIS): SSI in the secondary incision in a patient who has had an operation with more than 1 Incision (e.g., donor site [ant-sup iliac spine] incision for ACDF).

Deep Incisional SSI

1. Infection occurring within 30days of the operative procedure.
2. Involve deep soft tissues of the incision (fascial and muscle layers)

At least one of the following:

1. Purulent drainage from the deep incision.
2. A deep incision that spontaneously dehisces or is deliberately opened or aspirated by a surgeon, or an attending physician because of fever, localized pain, or tenderness.
3. An abscess or other evidence of infection involving the deep incision that is detected intraoperatively, or by radiological or Histopathologic examinations.

Deep incisional SSI is divided into two (2)
1. Deep Incisional Primary (DIP): SSI that is in a primary incision in a patient who has had an operation with one or more incisions.
2. Deep Incisional Secondary (DIS): SSI in the secondary incision in a patient who has had an operation with more than 1 incision (example donor's site [ant-sup iliac spine] incision for ACDF).

Organ/Space SSI

1. Infection occurs within 30days of the operative procedure and involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure.

Plus, one of the following:
1. Purulent drainage from a drain that is placed into the organ/space.
2. Organisms cultured from an aseptically obtained fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is detected intraoperatively or by radiological or histopathologic examinations.

Prevention of Surgical Site Infections

Prevention of Surgical site infections refer to any action or set of actions intentionally taken to reduce the risk of surgical site infection [30].

Over the past decades, various strategic interventions aimed at reducing the incidence of surgical site infections, and by extension its attendant associated morbidity, added financial cost and mortality were developed and implemented. Strategies were directed towards either enhancing the host defense system against infection such as identification and mitigation of modifiable risk factors, and those aimed at reducing the risk bacterial contamination of the surgical site and instruments such as preoperative skin preparation, sterilization of instrument, and strict aseptic techniques. Other adjuncts include antibiotic prophylaxis and meticulous surgical technique.

The patient skin's commensals is the primary source of bacterial responsible for surgical site infection [5], optimal preoperative antiseptic skin preparation is therefore crucial in preventing surgical site infections.

Preoperative Skin Antisepsis

Optimal antisepsis of the surgical site, which is the major source of pathogens, is an effective preventive measure of surgical site infection.

The goal of skin antisepsis in the surgical patient is to reduce the microbial burden on the surface of the skin to a sub pathogenic level before surgical incision, thereby reducing the risk of wound contamination.

An effective preoperative skin antiseptic, as defined in the US Food and Drug Administration document "Tentative Final Monograph for Healthcare Antiseptic Products," is an agent that rapidly (i.e., within 10 minutes of application) reduces the number of transient and resident microorganisms in the surgical field before wound incision and suppresses rebound growth for six hours after application [32]. In addition, it should be nontoxic and non-irritant.

The most commonly use antiseptic agents in neurosurgical procedures are 4% Chlorhexidine and 10% Povidone iodine [33].

10% Povidone iodine

Povidone-Iodine is a water-soluble iodophor (or iodine-releasing agent) which consists of a complex between iodine and a solubilizing polymer carrier, polyvinylpyrrolidone, which acts as a reservoir for ''free'' iodine (the active component). This unique complex was discovered in 1955 at the Industrial Toxicology Laboratories in Philadelphia by H. A. Shelanski and M. V. Shelanski [34,35].

The iodine is slowly released and delivered to the bacterial cell surface where it penetrates the cell membrane and inactivates key cytosolic proteins, fatty acids, and nucleotides.

Iodine has broad-spectrum antibacterial activity, as well as activity against fungi, protozoa, viruses, and some bacterial spores.

A drawback of povidone iodine is that, it is inhibited by blood, pus, fat, glove powder as well as protein containing solutions [34,35].

4% Chlorhexidine

Chlorhexidine is a polycationic bisbiguanide with broad spectrum antimicrobial activity discovered in 1954 [36]. Chlorhexidine damages the outer bacterial surface layers, thereby promoting its own uptake and subsequently attacking the cytoplasmic or inner membrane of the organism. The bactericidal effect because of the binding of the Chlorhexidine cationic molecules to negatively charged bacterial cell walls and extra microbial complexes.

At low concentrations, Chlorhexidine causes an alteration of bacterial cell osmotic equilibrium, resulting in leakage of potassium and phosphorus, and inhibits growth (i.e., it is bacteriostatic).

At high concentrations, Chlorhexidine produces a rapid bactericidal effect by causing the cytoplasmic contents of the bacterial cell to precipitate, resulting in cell death.

The advantage of chlorhexidine over povidone iodine is that it is not inactivated by blood or serum protein and exhibits a residual antimicrobial activity on the surface of the skin, suppressing microbial growth for several hours after application [34-36]. However, some of the side effects of chlorhexidine include skin rashes and allergy.

Chlorhexidine has a broad spectrum of activity that comprises gram-positive and gram-negative microorganisms, non-spore-forming bacteria, fungi, and lipid-enveloped virus, including human immunodeficiency virus (HIV) [36].

Combination of 4% Chlorhexidine and 10% Povidone Iodine

Because Chlorhexidine and povidone iodine have different cellular targets and different mechanisms of action, these differences may prove beneficial when using these two antiseptics in combination.

Chlorhexidine damages the outer membrane, which would augment access to the intracellular targets necessary for the bactericidal action of povidone iodine.

Studies have compared microbial counts after application of Chlorhexidine and povidone iodine alone and in sequential combination and concluded that the latter was more effective in reducing skin microbiota during preoperative preparation of the area of surgery.

Langgertner *et al.* in a randomized control trial in Germany, found bacterial growth of 30.8% against 4.7% from central venous catheter tip in patients who had preoperative skin preparation with Povidone iodine alone versus combined Chlorhexidine and povidone iodine respectively [37]. In another randomized control study at St Agnes Medical Centre Philadelphia, USA, involving 342 patients for allograft skin grafting, May and colleagues found residual bacterial contamination of 13.7% and 5.6% following skin preparation with povidone iodine alone versus combined Chlorhexidine and povidone iodine respectively [38].

Guzel and colleagues in Turkey, in a randomized control trial with 100 patients;50 patients going for Spine surgery and 50 going for cranial surgeries found residual bacterial contamination in 5% and 9% following skin preparation with chlorhexidine alone in spinal and cranial surgeries respectively. However, following addition of povidone iodine, the residual bacterial counts were 0% [39].

In a study at Queens University Medical Centre Belfast, United Kingdom, Patrick *et al* randomized 407 patients going for Spine surgeries and found residual bacterial contamination in 29.1% of patients who had preoperative skin antisepsis with povidone iodine alone, but 4.7% in those who had Chlorhexidine and Povidone iodine [40].

In a retrospective study, using rate of surgical site infection as primary outcome, involving 1146 patients that had cranial surgeries at Greater Manchester Neurosciences Centre United State, Davies and Patel found the rate of surgical site infection to be 3.2% in those who had preoperative skin antisepsis with Povidone iodine alone, but 0.9% in those who had combined Chlorhexidine and povidone iodine [41].

Conclusion

Reductions in both transient and resident pathogens, as well as the incidence of Neurosurgical surgical site infections are best achieved with sequential application of 4% Chlorhexidine and 10% Povidone iodine.

References

1. Bulander RE, Dunn DL, Balmin GJ. Surgical Infections. In: Brunicardi FC, Andersen DK, editor. Schwartz's Principle of Surgery. 1. USA: McGraw-Hall Education Foundation. 2019; 157-182.
2. Deverick AJ, Kelly P, Sandra IB, et al. Strategies to prevent Surgical site Infections in Acute Care Hospital: 2014 updates. Infection control and Epidemiology. 2014; 35: 606-627.
3. Klevens RM, Edwards JR, Chesley RL, et al. Estimating Health Care-Associated Infections and Death in U.S Hospitals, 2002. Public Health Rep. 2007; 122: 160-166.
4. Malomo AO, Adeolu AA, Odebode TO, et al. Prospective Comparative Trial of Ceftriaxone versus Ceftazidime as Prophylactic Perioperative Antimicrobials in Neurosurgery. East and Central African Journal of Surgery. 2007; 12: 89-92.
5. Zhan R, Zhu Y, Shen Y, et al. Post operative central nervous system infections after cranial surgery in china: incidence, causative agents, and risk factors in 1470 patients. Eur J Clin Microbiol Infect Dis. 2014; 33: 861-866.
6. O'Keeffe A, Lawrence T, Bojanic S. Oxford craniotomy infections database: a cost analysis of craniotomy infection. Br J Neurosurg. 2012; 26: 265-269.
7. Adeleye AO. Nonshaved cranial surgery in black Africans: technical report and a medium-term prospective outcome study. Neurosurg Rev. 2016: 1-6.
8. Taha MM, Abouhashem S, Abdel-Rahman AY. Neurosurgical Wound Infection at a University Hospital in Egypt; Prospective Study of 1181 Patients for 2 Years. Turkish Neurosurgery. 2014; 24: 8-12.
9. Shehu BB, Mahmud MR, Ismail NJ. Neurosurgical infections. Nigerian Journal of surgical Research. 2006; 8: 1-8.
10. Adeleye AO. Low rates of post-craniotomy surgical site infections in a developing country: surgical technique and results. British Journal of Neurosurgery. 2017; 32: 136-140.
11. Kitembo SK, Chugulu SG. Incidence of Surgical Site Infections and Microbial Pattern at Kilimanjaro Christian Medical Centre. The Annals of African Surgery. 2013; 10: 26-31.
12. Badia JM, Casey AL, Petrosillo N, et al. Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries. Journal of Hospital Infection. 2017; 96: 1-15.
13. Patricia LP, Cristina DP, Nieves LF, et al. Epidemiology of Surgical Site Infection in a Neurosurgery Department. British Journal of Neurosurgery. 2016; 31: 10-15.
14. Goran CB. Craniotomy Infections. Neurosurgery Clinics of North America. 1992; 3: 375-385.
15. Abu Hamdeh S, Birgitta L, Ronne-Engström E. Surgical site infections in standard neurosurgery procedures- a study of incidence, impact and potential risk factors. British Journal of Neurosurgery. 2014; 28: 270-275.

16. Fang C, Zhu T, Zhang P, et al. Risk factors of neuro- surgical site infection after craniotomy: A systematic review and meta-analysis. Am J Infect Control. 2017; 45: 123-134.
17. Emilio J, Guillermo C, Ana H, et al. Risk factors for surgical site infection after craniotomy: a prospective cohort study. Antimicrobial Resistance and Infection Control. 2019; 8.
18. Korinek AM, Golmard JL, Eicheick A, et al. Risk factors for neurosurgical site infections after craniotomy: a critical reappraisal of antibiotic prophylaxix on 4578 patients. British Journal of Neurosurgery. 2005; 19: 155-162.
19. Buang SS, Haspani MS. Risk Factors for Neurosurgical Site Infections After A Neurosurgical Procedure: A Prospective Observational Study at Hospital Kuala Lumpur. Medical Journal of Malaysia. 2012; 67: 393-398.
20. Yi-Fang M, Liang W, Yu Z. Prospective study evaluating post-operative central nervous system infections following cranial surgery. British Journal of Neurosurgery. 2019; 33: 80-83.
21. Martin N, Stienen NM, Philipp K, et al. Incidence, depth, and severity of surgical site infections after neurosurgical interventions. Acta Neurochirurgica. 2019; 161: 17-24.
22. Edmiston CE, Leaper D, Spencer M, et al. Considering a new domain for antimicrobial stewardship: Topical antibiotics in the open surgical wound. American Journal of Infection Control. 2017; 45: 1259-1266.
23. Mackenzie I. Preoperative Skin Preparation and Surgical Outcome. Journal of Hospital Infection. 1988; 11: 27-32.
24. Miller JT, Rahimi SY, Lee M. History of infection control and its contributions to the development and success of brain tumor operations. Neurosurg Focus. 2005; 18: 1-5.
25. Horan TC, Gaynes RP, Martone JW, et al. CDC Definations of Nosocomial Surgical Site Infection, 1992: A Modification of CDC Definations of Surgical Wound Infections. Infection control and Hospital Epidemiology. 1992; 13: 606-608.
26. Moiyadi AV, Sumukhi U, Shetty PM, et al. Scalp flora in Indian patients undergoing craniotomy for brain tumors – Implications for pre-surgical site preparation and surgical site infection. Indian Journal of Neurosurgery. 2012; 1: 28-32.
27. Dashti SR, Humain B, Robert ES, et al. Operative intracranial infection following craniotomy. Neurosurg Focus. 2008; 24: 1-5.
28. Chiang HY. Risk factors and outcomes associated with surgical site infections after craniotomy and craniectomy. University of Iowa. 2012.
29. Akhaddar A. Surgical site infections in Cranial Surgery. Atlas of Infections in Neurosurgery and Spinal surgery: Spinger. 2017; 191-215.
30. Mangram AJ, Horan TC, Pearson ML, et al. Guidelines for prevention of surgical site infection, 1999. AJIC. 1999; 27: 97-134.
31. Narotam PK, Van Dellen JR, Du Trevou DM, et al. Operative Sepsis in Neurosurgery: A Method of Classifying Surgical Cases Clinical Study. Neurosurgery. 1994; 34: 409-416.
32. Bobby S, Michael DJ, Hiren P, et al. Current preoperative antisepsis in neurosurgery: an example of the challenges in implementing evidence-based medicine to surgical practice. Annals of The Royal College of Surgeons of Englan. 2018: 1-6.
33. Ghobrial GM, Wang MY, Green BA, et al. Preoperative skin antisepsis with chlorhexidine gluconate versus povidone-iodine: a prospective analysis of 6959 consecutive spinal surgery patients. Journal of Neurosurgery Spine. 2017: 1-6.
34. McDonnell G, Russell DA. Antiseptics and Disinfectants: Activity, Action, and Resistance. Clinical Microbiology Review. 1999; 12: 147-179.
35. Negash A, Mohammed N. Common Antiseptics: Mechanism Of Action And Its Uses In Animal. Nature and Science. 2016; 14: 52-56.
36. Milstone AM, Passaretti CL, Perl TM. Chlorhexidine: Expanding the Armamentarium for Infection Control and Prevention. Healthcare Epidemiology. 2008; 46: 274-281.
37. Langgartner J, Linde H, Lehn N, et al. Combined skin disinfection with chlorhexidine/propanol and aqueous povidone-iodine reduces bacterial colonisation of central venous catheters. Intensive Care Med. 2004; 30: 1081-1088.
38. May SR, Roberts DP, DeClement FA, et al. Reduced bacteria on transplantable allograft skin after preparation with chlorhexidine gluconate, povidone-iodine, and isopropanol. Journal of Burn Care Rehabilitation. 1991; 12: 224-228.
39. Guzel A, Ozekinci T, Ozkan U, et al. Evaluation of the skin flora after chlorhexidine and povidone-iodine preparation in neurosurgical practice. Surgical Neurology. 2009; 71: 207-210.
40. Patrick S, McDowell A, Lee A, et al. Antisepsis of the skin before spinal surgery with povidone iodine-alcohol followed by chlorhexidine gluconate-alcohol versus povidone iodine-alcohol applied twice for the prevention of contamination of the wound by bacteria. The Bone & Joint Journal. 2017; 99: 1354-1365.
41. Davies BM, Patel HC. Does chlorhexidine and povidone-iodine preoperative antisepsis reduce surgical site infection in cranial neurosurgery?. Annals of the Royal College of Surgeons of England. 2016: 1-4.