ABSTRACT

Introduction: Chlorhexidine 4% gel is specifically formulated for umbilical cord care and is safe and effective for reducing bacterial colonization on the skin and umbilical stump of the newborn. 7.1% chlorhexidine digluconate delivering 4% chlorhexidine was added to the 2013 World Health Organization (WHO) List of Essential Medicines for Children, specifically for umbilical cord care. Chlorhexidine can induce allergic contact dermatitis, immediate type hypersensitivity reaction, urticaria, photosensitivity, chemical burns and maculopapular erythema. Method: Hospital based descriptive and observational study was carried out in Paropakar Maternity and Women’s Hospital, Thapathali. The study was carried out for 5 months from September 2017 to February 2018. Total of 300 newborns whose umbilical cord was about to be removed were included in the study. Chlorhexidine gluconate gel was applied immediately after the removal of umbilical cord for the prophylactic treatment of umbilical cord infection. The newborns were observed for any adverse effects of drug and the suspected case of ADR was assessed by using Naranjo’s ADR Probability Scale. Newborns were followed up during their stay in hospital. The newborns who were died before removal of umbilical cord, who were transferred to NICU and those newborns whose guardians were unwilling to participate were excluded from the study.

Result: Among 300 newborns, there were 168 male and 132 female newborns. In the study group, 8.33% newborns were preterm and 91.67% were term newborns. The lowest weight of newborn was 1400 gm and highest weight was 4800 gm. On observation of the cord after the application of chlorhexidine 4% gel, among 300 newborns, no newborn showed adverse reaction to chlorhexidine. Conclusion: Chlorhexidine 4% gel was applied to umbilical cord
of newborns and no adverse reaction was observed on single application of the drug. Hence the drug is safe for newborns.

**KEYWORDS:** Chlorhexidine, newborns, umbilical cord, adverse drug reaction.

**INTRODUCTION**

**1.1. Background**

Of the 4 million annual neonatal deaths that occur globally, more than 99% occur in developing countries and approximately 36% are attributed to infections such as sepsis, meningitis, pneumonia, omphalitis, tetanus, and diarrhea.\[1,2\] Umbilical infections are important cause of neonatal morbidity and mortality in developing countries with incidence rates as high as 55-197 per 1000 live births in community-based studies.\[3\] In neonates, umbilicus acts as a bacterial reservoir and a potential entry point for the infection, especially in first few days of life, when umbilical vein is patent. This may lead to sepsis with or without omphalitis.\[4\]

Omphalitis, an infection of the umbilical stump, resulting from colonization of the stump with bacteria from the maternal genital tract and the environment poses a significant risk of infection and death during the first 28 days of life.\[5\] Organisms such as *Staphylococcus aureus*, group A and group B *Streptococci* and Gram-negative bacilli including *Escherichia coli*, *Klebsiella* species, and *Pseudomonas* species and rarely anaerobes are responsible for umbilicus infections.\[6\] The local signs of umbilical cord infection include pus, redness, swelling, warmth, tenderness and foul odor.\[4\] Unclean deliveries and unhygienic cord care practice such as using unclean tools to cut the cord, using roots or chewed bark fibers to tie it, or covering the cord with ashes, herbs, animal dung or mustard oil can increase the risk of omphalitis.\[7\]

Since 1998, the WHO has recommended promotion of clean and dry cord care for newborn infants, while noting that topical antiseptics may be used where risk of infections is high.\[8\] Antiseptic substances have been applied to the skin and umbilical cord stumps of newborn babies for many years for controlling bacterial colonization and reducing the prevalence of neonatal infection.\[9\] Umbilical cord cleansing with 4% chlorhexidine can substantially reduce neonatal mortality among newborn infants in low-resource settings with high risk of infection.\[10\]
1.2. Chlorhexidine Pharmacology

Chlorhexidine is a topical antiseptic having broad-spectrum activity against Gram-positive organisms (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Bacillus subtilis* etc.), Gram-negative organisms (*Bacteroides fragilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* etc.), and fungus (*Penicillium notatum*, *Aspergillus niger*, *Candida albicans* etc.).[11,12] Chlorhexidine has an extensive safety record, strong binding potential that results in residual effectiveness, and low cost.[13] If topically used, Chlorhexidine covalently binds to cutaneous and mucosal proteins resulting in a persisting antimicrobial effect with limited systemic absorption, even after its oral ingestion.[14]

**Mechanism of Action**

Chlorhexidine has bacteriostatic, bactericidal, fungicidal, fungistatic and some virus killing properties. Chlorhexidine is adsorbed onto phosphate containing protein components in the bacterial cell wall. At bacteriostatic concentrations, it penetrates and disrupts the bacterial cytoplasmic membrane resulting in leakage of cytoplasmic components. At higher concentrations it exerts a bactericidal action by forming irreversible precipitates with intracellular adenosine triphosphate and nucleic acids after entering the cytoplasm via the damaged cytoplasmic membrane. Minimum inhibitory concentrations are lower for Gram-positive bacteria than for Gram negative bacteria because chlorhexidine has an increased affinity for cell wall of Gram Positive organisms.[12]

![Mechanism of Action](image.png)
Chlorhexidine Gel

Chlorhexidine 4% gel is specifically formulated for umbilical cord care and is safe and effective for reducing bacterial colonization on the skin and umbilical stump of the newborn.\[16\]

![Chlorhexidine 4% gel (Kawach Navi Malham).](image)

7.1% chlorhexidine digluconate was added to the 2013 World Health Organization (WHO) List of Essential Medicines for Children, specifically for umbilical cord care. In January 2014, the WHO issued a new recommendation for umbilical cord care. “Daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births).\[17\]

Chlorhexidine topical application on cord stump has been shown to decrease umbilical colonization, umbilical sepsis and thus possibly systemic sepsis.\[18\] Randomized trials in Nepal, Bangladesh and Pakistan have demonstrated mortality reduction ranging from 6% to 38% among live-born infants receiving single or multiple cleansing within the first days of life.\[10\]

Chlorhexidine gluconate (CHG) has been shown to be safe and well tolerated in term neonates exposed to chlorhexidine by different methods, including via vaginal washings, umbilical cord cleansing and whole-body cleansing. Although there is some evidence documenting the safety of CHG in term infants, there is still a gap in the existing data regarding the safety and impact of CHG in preterm infants. Preterm infants, especially those <32 weeks gestation, have immature skin with increased permeability, vulnerable developing neurological systems and metabolic limitations resulting in decreased drug clearance; all of which might predispose them to a higher rate of adverse reactions from CHG.\[19\]
1.3. Adverse Drug Reaction

Drugs are a dualistic therapeutic tool intended to cure, prevent or diagnose diseases, signs or symptoms, but the shadow side is that no drug is absolutely safe under all circumstance of use or in all patients and ADR may occur even if a drug is correctly selected and dosed.\textsuperscript{[20,21]}

An ADR is defined by the World Health Organization (WHO) as “any response to a drug which is noxious, unintended, and that occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function.”\textsuperscript{[22]} ADRs can worsen a patient’s medical problems, place patients in life-threatening situations and extend patients length of stay in hospital thus leading to increased healthcare costs.

Lazarou et al. found the overall incidence of serious ADRs in the general hospitalized population of the USA to be 6.7%. The incidence of fatal ADRs was 0.32% amongst patients from 39 prospective studies included in this meta-analysis. Thus, ADRs are likely to be between the fourth and sixth leading cause of death in the USA.\textsuperscript{[23]}

Classification of ADR

Adverse Drug Reactions are classified into five types.

a. Type A Reactions (augmented): Result from an exaggeration of a drug’s normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent. E.g. respiratory depression with opioids or bleeding with warfarin.

b. Type B Reactions (bizarre): Novel responses that are not expected from the known pharmacological actions of the drug. These are less common, and so may only be discovered for the first time after a drug has already been made available for general use. E.g. anaphylaxis with penicillin or skin rashes with antibiotics.

c. Type C Reactions (continuing): Persist for a relatively long time. E.g. osteonecrosis of the jaw with bisphosphonates.

d. Type D Reactions (delayed): Become apparent sometime after the use of a medicine. E.g. leucopenia, which can occur up to six weeks after a dose of lomustine.

e. Type E Reactions (end-of-use): Associated with the withdrawal of a medicine. E.g. insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines.\textsuperscript{[24]}
Type A adverse drug reactions are more common than type B reactions, accounting for over 80% of all reactions.\cite{25}

**Hartwig severity assessment scale**

As per this scale ADRs are classified as follows.

1. Mild reactions which are self-limiting and able to resolve over time without treatment and do not contribute to prolongation of length of stay.
2. Moderate ADRs are defined as those that requires therapeutic intervention and hospitalization prolongs by 1 day but resolves in < 24h or change in drug therapy or specific treatment to prevent a further outcome.
3. Severe ADRs are those that are life threatening, producing disability and those that prolongs hospital stay or led to hospitalization, required intensive medical care, or led to the death of the patient.\cite{26}

**Gell and Coombs Classification of Drug Hypersensitivity Reactions**

1. Type I (IgE-mediated):
   - Drug-IgE complex binds to mast cells with release of histamine, inflammatory mediators. Example: urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis
2. Type II (cytotoxic):
   - Specific IgG or IgM mediated. Example: Hemolytic anemia, neutropenia, thrombocytopenia.
3. Type III (immune complex reactions)
   - IgG and IgM mediated. Example: Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis.
4. Type IV (delayed type)
   - Cell-mediated reactions. Example: Allergic contact dermatitis, maculopapular drug rash.\cite{27,28}

Chlorhexidine can induce allergic contact dermatitis, immediate type hypersensitivity reaction, urticaria, fixed drug eruption, photosensitivity, chemical burns and maculopapular erythema.\cite{1,14,29,30} Contact allergy is a T-cell mediated allergy characterized by contact dermatitis at the skin site of contact. The pathophysiological mechanism can be divided into two phases: an induction phase, where the allergy is developed (also called sensitization phase); and an elicitation phase, where re-exposure to the allergen can cause allergic
symptoms such as erythema, infiltration and edema.\cite{31}

1.4. Pharmacovigilance

WHO defines, “Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem”.\cite{32} It is the process of identifying and responding to the issues of drug safety through adverse effects. It is aimed for detection of severe and unexpected adverse drug reactions to the established drugs and even the minor ones to newer drugs and for identification of the risk factors associated with the development of adverse drug reactions and mechanisms of their causation.\cite{27} Post marketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of pharmacovigilance.\cite{33}

Pharmacovigilance in Nepal

In the year 2004, pharmacovigilance activities were initiated in Nepal which became a full member of the international pharmacovigilance programme in 2007. The Department of Drug Administration (DDA), the national drug regulatory authority of Nepal acts as the national center for ADR monitoring. In Nepal, hospitals report ADRs to the regional pharmacovigilance centers from where reports are sent to the national pharmacovigilance center. From there reports are sent to the Uppsala Monitoring Centre (UMC), Sweden, the international center. At present, there are six regional pharmacovigilance centres located in teaching hospitals which report ADRs to the national center via a web-based system called ‘Vigiflow’.\cite{34}

1.5. Prevalence of ADR of Chlorhexidine

Contact allergy to chlorhexidine was first described in 1962.\cite{31} Contact dermatitis was reported in 5% of preterm (< 28 weeks' gestation) extremely low-birthweight (< 1000 g) infants after long-term (> 7 days) placement of chlorhexidine-impregnated dressings for central venous catheters. The effect may have been caused by the occlusive placement of the dressing rather than the chlorhexidine itself; in the same study, no infants receiving a preplacement scrub with 0.5% chlorhexidine developed dermatitis. Contact dermatitis has not been reported in infants receiving full-body wiping, bathing, or umbilical cord cleansing with chlorhexidine. Transient bradycardia was reported in a breast-fed infant whose mother's breast was sprayed with chlorhexidine.\cite{1}
Immediate-type chlorhexidine allergy is rare, but the prevalence in the general population remains unknown. Most of the case reports on chlorhexidine allergy include patients who had allergic reactions during surgery, where exposure is high, and it was recently found that 5% (UK), and 8.6% (Netherlands), respectively, of all patients with a suspected perioperative allergic reaction were diagnosed with chlorhexidine allergy. In 2007, it was confirmed that there is an IgE-mediated mechanism behind immediate-type chlorhexidine allergy.\textsuperscript{[31]}

1.6. Rationale of the study

When people use medications, any number of outcomes are possible. Most commonly, the patient benefits from pharmacotherapeutic interventions; however, adverse events, ranging from minor side effects to death, may occur.\textsuperscript{[35]} According to DJP Barker, “There are three actions of a drug: The one you want, the one you don’t want, and the one you don’t know about”. Also, detection of ADRs has become increasingly significant because of introduction of large number of potent toxic chemicals as drug in last two or three decades. Thus, it becomes very crucial to monitor both known and unknown adverse effects of medicines.\textsuperscript{[36]} Chlorhexidine gluconate 4% gel is a new formulation particularly for umbilical cord care in newborn babies. Nepal is the first country to have registered a chlorhexidine product specifically for umbilical cord stump care. Additionally, Nepal has included chlorhexidine in their 2011 national list of essential medicines.\textsuperscript{[37]}

The study on the skin effects of CHG in neonates is very limited. The premature infant has a poor epidermal barrier with few cornified layers and is at risk for increased permeability to exogenous materials, additional skin compromise, delayed barrier maturation and infection. The dermis is deficient in structural proteins and the skin is easily torn.\textsuperscript{[38]} This might predispose them to higher rate of adverse reactions to CHG.

Chlorhexidine gluconate 4% gel for umbilical cord care being a new formulation, it is essential to identify any adverse drug reactions. Hence, the main aim of this study is to identify, assess and manage adverse drug reaction of chlorhexidine gluconate gel.

1.7. RESEARCH OBJECTIVES

1.7.1. General Objective

1. To study the adverse drug reactions of chlorhexidine 4% gel used for umbilical cord care in newborns.
1.7.2. Specific Objectives

1. To identify the risk factors for adverse reaction of Chlorhexidine Gel (such as gestation period, gender, weight and medical condition of newborns).
2. To identify the incidence of ADR and manage the ADR of chlorhexidine 4% gel in newborns.
3. To estimate the burden of ADR (length of hospital stay due to ADR, cost)

LITERATURE REVIEW

Garland et al. carried out a study on “A Randomized Trial Comparing Povidone-Iodine and a Chlorhexidine Gluconate Impregnated Dressing for Prevention of Central Venous Catheter (CVC) Infection in neonates” and reported severe contact dermatitis with the use of a CHG-impregnated dressing that was placed over catheter sites after insertion. During the study period, 15 (15%) of 98 infants < 1000g and 4 (1.5%) of 237 infants ≥1000 g who received the CHG dressing developed related contact dermatitis under the dressing. Most episodes of dermatitis occurred in neonates who were < 28 weeks gestation at birth and less than a week old. These episodes of dermatitis may have been secondary to CHG, but some have suggested that external pressure from an occlusive adhesive dressing may restrict capillary perfusion to the skin and cause local skin breakdown.[39, 40]

Chapman AK. and et al carried out a study on “Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates”. The objective of the study was to assess chlorhexidine absorption and skin tolerability in premature infants, following skin antisepsis with 2% aqueous chlorhexidine gluconate (CHG) prior to peripherally inserted central catheter (PICC) placement. Twenty preterm neonates were exposed to CHG. The median gestational age was 28 2/7 weeks (range 24 3/7 to 31 4/7) and median birth weight was 925 g (range 630 to 1735). Ten infants had detectable serum chlorhexidine concentrations (range 1.6 to 206 ng ml). Seven of these infants had their highest serum concentration 2 to 3 days following exposure. No CHG-related skin irritation occurred in any infants.[41]

Tamma PD. and et al carried out a national survey on Chlorhexidine use in the Neonatal Intensive Care Unit with the objective to assess the practice of CHG use in United States NICUs and to understand real and perceived safety concerns of CHG in neonates. Of the 55 NICU’s that utilized CHG, the most commonly reported use was CVC maintenance (78%), including dressing changes and catheter hub cleaning. Other uses of CHG included CVC
insertion site preparation (70%), peripheral venous catheter insertion (60%), and skin preparation for umbilical catheter insertion (51%). They found that twenty-eight participants (51%) who used CHG in their NICU reported adverse reactions. All were skin reactions and included erythema (32%), erosions (7%), or burns (61%). Of the reported skin burns, 13 of 17 (76%) commented that the burns occurred in neonates with a birth weight of less than 1500 grams; the other four did not comment on the infant’s birth weights.[42]

_Lashkari HP. and et al_ carried out a study on **Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant.** Chlorhexidine gluconate 2.0% w/v aqueous solution (Aquix 2%) was used to prepare the skin before umbilical catheter insertion soon after birth in a non-identical preterm twin born at 25+4 weeks gestation. Two hours later, the skin in the right iliac fossa, right flank, the periumbilical area, perineum and groin turned erythematous. Over the subsequent 6 h, the skin became pale. The epithelium was lost in the affected areas, and the appearance was consistent with mixed-depth, partial-thickness burns. These injuries completely healed with conservative management over 4 weeks with no residual scarring. Interestingly, the other twin, who also needed umbilical catheter placement, did not develop any burns as the antiseptic solution was entirely wiped off with normal saline immediately after skin sterilization.[30]

In 1981, _Aggett et al._ assessed CHG absorption in 25-term infants and 23-preterm infants with gestational ages between 31 to 36 weeks. After birth, the infants had repeated treatments of a 1% CHG in ethanol solution and a 1% CHG with 3% zinc oxide powder placed on their umbilical cord stumps every 4 h for at least 9 days. Significantly higher concentrations of chlorhexidine were seen in the preterm infants compared with the term infants on days 5 and 9, as well as a significant increase in chlorhexidine concentrations from day 5 to day 9 in the preterm infants, suggesting possible accumulation. Although there were no adverse events reported, this study demonstrated increased absorption in preterm infants compared with term infants.[19]

**METHODOLOGY**

**3.1. Study design**

The study is a descriptive and observational type of study which was undertaken at Paropakar Maternity and Women’s Hospital located in Thapathali, Kathmandu, Nepal. The term and preterm healthy newborns delivered during the study period were included in this study and the effect of chlorhexidine 4% gel applied in umbilical cord immediately after the birth was
observed. The umbilical cord of newborns was observed for any signs of adverse drug reaction of chlorhexidine 4% gel during their stay in hospital.

**Study duration**: The study was carried out for the period of 5 months from September 2017 to February 2018.

**Sample size**: 300.

### 3.2. Institutional Consent

An institutional approval was taken from Institutional Review Board of Paropakar Maternity and Women’s Hospital, and permission from the concerned authorities was taken before study. Prior to collection of data, written consent was taken from the guardians of newborns for the study. The identity of the newborns was not disclosed. All the research activities were carried out under the close guidance of supervisors.

### 3.3. Study Variables

**Dependent**: Newborns  
**Independent variables**: Chlorhexidine gel and its adverse effect, gestation period of the newborns, weight of the newborns, medical condition of newborns.

### 3.4. Inclusion criteria

- Live birth whose umbilical cord was not removed but about to remove.

### 3.5. Exclusion criteria

- Babies who died before removal of umbilical cord.  
- Babies who were transferred to NICU.  
- Those newborns whose guardians were unwilling to participate in the study.

### 3.6. Data collection technique and tools

Chlorhexidine 4% gel, provided by Nepal Government to the hospital, was used for the prophylactic treatment of umbilical cord infection. The gel was applied to the umbilical cord of newborns by the duty nurses.

The data for the study was collected from the mothers admitted to the ward after the delivery. The newborns were followed up during their stay in hospital. Any effect of chlorhexidine 4% gel applied to the cord stump for prophylactic treatment of possible infections was observed.
Structured questionnaire was used as a tool for collection of information through interview with mothers of newborns during the hospital stay. The suspicious condition of adverse drug reaction was assessed using Naranjo’s ADR Probability Scale. To avoid bias, the observation of cord for the detection of adverse reaction of chlorhexidine 4% gel, was performed with the help of duty nurses and doctors.

Data entry was done using Microsoft Excel.

Table 1: Naranjo ADR probability scale for causality assessment.[26]

<table>
<thead>
<tr>
<th>Naranjo Adverse Drug Reaction Probability Scale</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse event reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Causality assessment score Definite: ≥9.
Probable: 5–8.
Possible: 1–4 Doubtful: ≤0.
RESULTS AND DISCUSSION

4.1. Gestation Period and Gender distribution of newborns

A total of 300 newborns were included in the study out of which 25 (8.33%) newborns were preterm (i.e. <37 weeks) while 275 (91.67%) newborns were term (i.e. >37 weeks). The lowest gestation period was 232 days (33\text{\textfrac{1}{2}}\text{ weeks}) and highest gestation period was 303 days (43\text{\textfrac{2}{2}}\text{ weeks}). The highest number of newborns were found in the gestation period of 281-285 days which made up the 22% of total number of newborns. This study is similar to the study done by P. C. Nayana Prabha et al on Effectiveness of Chlorhexidine in Prevention of Umbilical Sepsis which shows highest number of newborns above 37 weeks (259 days) of gestation.\[^{[43]}\]
4.2. Gender of newborns

Among 300 newborns, there were 168 (56%) male and 132 (44%) female newborns. This study is similar to the study done by Sajawal S. et al in Tanzania (51.1% Male and 48.9% female) (44).

4.3. Weight of the Newborns

Among 300 newborns, the lowest weight of the newborn was 1400 gm while the highest weight was 4800 gm. The average weight of the newborns was found to be 3013.15 gm.
4.4. Delivery Type

![Figure 7: Delivery Type.](image)

Among 300 newborns, 166 newborns were born by normal delivery while 134 newborns were born by cesarean delivery.

4.5. Medical Condition of Newborns

![Figure 8: Medical Condition of Newborns.](image)

Out of 300 newborns, 292 (97.3%) newborns were active, alert and had stable vitals but 8 (2.7%) newborns were suffering from fever. On detailed examination of baby’s condition, it was found that fever was not due to adverse effect of chlorhexidine 4% gel, but vaccination and other factors were found to be responsible for fever.
Table 3: Observation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported ADR(^1,14,29,30)</th>
<th>Management</th>
<th>ADR of CHG 4% gel found from the study</th>
<th>Burden of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine</td>
<td>● Contact dermatitis</td>
<td>Wipe off the drug with cotton swab dipped in lukewarm water or normal saline</td>
<td>Not seen</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>● Immediate-type hypersensitivity reaction</td>
<td></td>
<td>Not seen</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>● Urticaria</td>
<td></td>
<td>Not seen</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>● Photosensitivity</td>
<td></td>
<td>Not seen</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>● Chemical burns</td>
<td></td>
<td>Not seen</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>● Erythema</td>
<td></td>
<td>Not seen</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 4: WHO-UMC Causality Categories\(^{45}\)

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria*</th>
</tr>
</thead>
</table>
| Certain              | • Event or laboratory test abnormality, with plausible time relationship to drug intake  
|                      | • Cannot be explained by disease or other drugs                                        
|                      | • Response to withdrawal plausible (pharmacologically, pathologically)                
|                      | • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) 
|                      | • Rechallenge satisfactory, if necessary                                              |
| Probable/Likely      | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
|                      | • Unlikely to be attributed to disease or other drugs                                  
|                      | • Response to withdrawal clinically reasonable                                        
|                      | • Rechallenge not required                                                             |
| Possible             | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
|                      | • Could also be explained by disease or other drugs                                    
|                      | • Information on drug withdrawal may be lacking or unclear                             |
| Unlikely             | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)  
|                      | • Disease or other drugs provide plausible explanations                                  |
| Conditional/Unclassified | • Event or laboratory test abnormality                                          
|                      | • More data for proper assessment needed, or                                         
|                      | • Additional data under examination                                                  |
| Unassessable/Unclassifiable | • Report suggesting an adverse reaction                          
|                      | • Cannot be judged because information is insufficient or contradictory                
|                      | • Data cannot be supplemented or verified                                            |

*All points should be reasonably complied with
PHOTO GALLERY

Figure 1: Cord Observation Immediately after CHG application.

Figure 2: Cord Observation on 2nd day of CHG application.

Figure 3: Cord Observation after few days of CHG application.

DISCUSSION

Chlorhexidine is a broad-spectrum antiseptic, effective against major agents of neonatal sepsis. Since its development in 1950, chlorhexidine has been widely used in a range of applications including hand washes, preoperative body shower, wound care, cosmetics, oral hygiene, general disinfection, and veterinary care.\[^{37}\] It has also been used in obstetrics, peripartum, perineal and vaginal washes in concentrations as high as 4%. Chlorhexidine is currently included in WHO’s Essential Drugs List and is the antiseptic of choice for cord care in newborns.\[^{8}\]

Chlorhexidine based products are available at a concentration from <1% to 20%.\[^{37}\] In my study, Chlorhexidine 4% gel was applied to umbilical cord of newborns as a prophylactic treatment of umbilical cord infections. Among 300 newborns, majority of newborns were of gestation period 281-285 days and 25 newborns were preterm while 275 were term. Out of
300 newborns 56% were male and 44% were female. The average weight of newborns was found to be 3013.15gm.

When the umbilical cord was observed after application of chlorhexidine gluconate gel, among 300 newborns, no newborn shown adverse reaction to Chlorhexidine 4% gel. This result is similar to the study conducted by Gathwala G. in India.[18]

Any suspicious condition was assessed using Naranjo’s ADR Probability Scale. Among 300 newborns, 2.8% were suffering from fever but on assessment with Naranjo’s scale, occurrence of fever was found to be due to other causes than adverse effect. Thus, adverse effect of Chlorhexidine 4% gel used for prophylactic treatment of possible infection in newborns is doubtful (i.e. Causality Assessment Score from Naranjo’s ADR Probability Scale was found to be “0”) for single application. But WHO recommends daily chlorhexidine application to the umbilical cord stump during the first week of life for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births) [17] hence ADR might be more likely to occur on multiple application.

CONCLUSION
This study was undertaken to identify, assess and manage the adverse drug reaction of chlorhexidine 4% gel applied in umbilical cord of newborns for prophylactic treatment of cord infection. As found from the study, chlorhexidine 4% gel for umbilical cord care is safe for newborns. But as found from the literature, the risk factors for the adverse reaction of chlorhexidine gel are preterm newborns and newborns with low birth weight, so in this case chlorhexidine 4% gel should be used with caution and with routine examination of umbilical cord.

LIMITATIONS OF THE STUDY
1. The data was collected only from Paropakar Maternity and Women’s Hospital, so the data cannot be generalized.
2. The sample size of the study is small which may not be sufficient to represent the entire newborns of Nepal.
3. Study is mattered being concern to time, financial resource to make the study more valuable and reliable.
RECOMMENDATIONS

- Similar type of research should be conducted throughout the country especially in rural areas.
- Adverse drug reactions of Chlorhexidine gel after multiple application can be studied.
- Continuous education about use of chlorhexidine gel to every mother in low resource settings.
- Similarly, adverse drug reaction of other drugs can be studied.

REFERENCES


23. Routledge PA, O'mahony M, Woodhouse K. Adverse drug reactions in elderly patients.


27. DABHADE SUHAS BDD, ATRE KAVITA. REVIEW ON PHARMACOVIGILANCE STUDY OF TELMISARTAN IN HYPERTENSION PATIENTS. Asian Journal of Pharmaceutical and Clinical Research, 2013; 6(3).


**ANNEX**

**DATA COLLECTION FORM**

<table>
<thead>
<tr>
<th>Date of Admission:</th>
<th>Date of Discharge:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Medical record number:</th>
<th>Weight (kg):</th>
<th>Religion: Gestation Period:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s Name:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs.):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history:</td>
<td></td>
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</tr>
<tr>
<td>Medication history:</td>
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<tr>
<td>Provisional diagnosis:</td>
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<table>
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<tr>
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<th>Time of birth:</th>
<th>Weight:</th>
</tr>
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<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>Gender of baby:</td>
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<tr>
<td>Medical condition:</td>
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</tbody>
</table>

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**1553**
Date of CHX gel application: Date of cord observation:
Onset of reactions (if any):
Address: Contact no.:
Length of Hospital stay:
Note:

Laboratory Investigations of Mother:

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<thead>
<tr>
<th>Current Drugs</th>
<th>Dose</th>
<th>Route</th>
<th>Freq.</th>
<th>Day1</th>
<th>Day2</th>
<th>Day3</th>
<th>Day4</th>
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</thead>
<tbody>
<tr>
<td>Discharge medications:</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Follow Up / Review</td>
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</tr>
</tbody>
</table>

PATIENT CONSENT FORM

NATIONAL MODEL COLLEGE FOR ADVANCE LEARNING NAYABAZAR, KATHMANDU

Subject: Study on Adverse Drug Reaction of Chlorhexidine gel for umbilical cord care in newborns.

I am a Bachelor student of Pharmacy in National Model College for Advance Learning (NMCAL) under Tribhuvan University. This study is being conducted for the partial fulfillment of degree of Bachelor of Pharmacy. The purpose of the study is to identify and assess the adverse drug reaction of chlorhexidine gel used for prophylactic treatment of possible infection of umbilical cord in newborns. I am going to observe your baby’s umbilical cord to see any changes after application of chlorhexidine gel and I will be using other information and case sheet. The success of the study depends on your full participation, so I would like to request you to participate in the study.

Thanking You

Name of the investigator: Name of the Legal Guardian.

Signature of the Legal Guardian.