ORIGINAL ARTICLE

How is oxytocin cold chain in peripheral areas and is it still effective uterotonic?

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ABSTRACT

Background. World Health Organization (WHO) has recommended oxytocin as an optional uterotonic medicine to prevent and handle postpartum haemorrhage. However, there is much worry about the quality of oxytocin in developing countries.

Aim: To describe the condition of oxytocin cold chain in the peripheral area, from the source until before being applied to the patients.

Method. Mixed method with sequential exploratory strategy was used in this study. Qualitative design used phenomenological approach and quantitative method used cross-sectional approach. Data collecting was done through in-depth interviews using interview guidelines. Participants were oxytocin suppliers, persons in charge of drug warehouses in medical centres, and medical personnels helping childbirth. Samples were selected using purposive sampling. Data collecting was done from November 2017 to February 2018 in Indragiri Hilir Regency, the Province of Riau, Indonesia. There were 32 participants getting involved in in-depth interviews, 123 respondents filled in questionaires and all were verified using supporting data.

Results. Findings of this study describe oxytocin cold chain including drugstores, delivery process, duration of delivery, oxytocin handling, oxytocin orders, kinds of medicine, medicine chests, and electricity in medicine supliers, drug warehouses and medical centres.

Conclusion. Most of the cold chain of oxytocin is not maintained from drug suppliers, drug warehouses, health care providers to the patients. Deviation tolerance of oxytocin cold chain can not be used as a justification. There is a consequence of oxytocin potential decline for every deviation. The government should examine unregistered and below standard medicine manufacturers, and encourage law enforcement for every violation.

Keywords: Cold chain, oxytocin, delivery, storage

INTRODUCTION

Up to now, the world's attention is still focusing on postpartum haemorrhage as the main cause of mother's mortality, particularly in developing countries[1]. Postpartum haemorrhage is defined as loss of blood ≥500 mL in the first 24 hours after giving birth and loss of blood ≥1000mL as severe postpartum haemorrhage in the same period of time[2]. The most common cause of haemorrhage is uterine atonia[3]. Some findings prove that the use of uterotonic prophylaxis in active management of third stage of labour with proper time and management can reduce the risk of postpartum haemorrhage[2, 4, 5]. World Health Organization (WHO) has recommended oxytocin as an optional uterotonic medicine that can be used routinely in active management of third stage of labour[2, 6] and considered it a golden standard[2] to prevent and handle postpartum haemorrhage[2, 7].

Besides, oxytocin has also been put in the list of WHO essential medicine model since it was firstly published in 1997[8-10].

Oxytocin is a peptide[11] which has a thermolabile characteristic[12-14] available in the form of solution kept in ampuls and it needs cold chain of storage, sterile needles with a special waste bin, and professional health personnels[15]. In order to maintain the effectiveness of medicine, International Pharmacopoeia recommends the storage of oxytocin in temperature of 2-8ºC, and suggests to protect it from sun exposure[12, 16] and to avoid the risk of being frozen during storage because it can make the medicine unstable[17]. To prevent bleeding, oxytocin must be applied as soon as possible after childbirth[2, 4]. International Confederation of Midwives (ICM) and International Federation of Gynaecology and Obstetrics (FIGO) recommend to administer oxytocin in 1 minute after childbirth[18]. Therefore, skillful health personnels and safe practice of injection are crucial points, as well as the availability of proper cooler chests for oxytocin storage to maintain the stability of the medicine[7]. Health personnel's skill is not optimum to reduce the risk of mortality, which is caused by bleeding, if it is not supported by high quality medicine.

Nowadays, oxytocin has become one of three uterotonic medicines which are most frequently used in countries with low and medium income per capita[10]. However, there is much worry about the quality of oxytocin in such countries. The main worry related to the use of oxytocin is inconsistent and unreliable cold storage[6] and low quality of manufacture or improper transportation and storage. Oxytocin without cold storage will get damaged, especially in tropical climate[6]. This study aims to describe the condition of oxytocin cold chain in the peripheral area, from the source until before being applied to the patients. Findings of the study are expected to become feedbacks for the government and health personnels in order to improve the efective use of oxytocin as an optional uterotonic medicine to prevent and handle postpartum haemorrhage and as an effort to improve the quality of health service for the society.

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METHOD OF STUDY

Mixed method with sequential exploratory strategy was used in this study where it was started with qualitative study and followed by quantitative study. The qualitative study used phenomenological approach to explore the oxytocin condition starting from the order until the application of oxytocin to the patients during active management of third stage of labour. Data collecting was carried out through in-depth interviews using interview guidelines which were constructed from three previous interviews. In-depth interviews were done after getting the approval from the participants, including approval to record all conversation during interviews. The participants in this study were oxytocin suppliers, persons in charge of drug warehouses in health centres, and medical personnels helping childbirth in hospitals, public health centres, assigning public health centres, childbirth clinics, independent-practice midwives. Samples selection used purposive sampling technique. After getting the information about the condition of oxytocin, the outcome was confirmed using quantitative study. The quantitative design used cross-sectional approach. This study was used to generalize the condition of oxytocin cold chain in the area. Data collecting was carried out from November 2017 to Februari 2018 in the area of Indragiri Hilir Regency, the Province of Riau, Indonesia. There were 32 participants getting involved in the thorough interviews; they were 1 person in charge of Regency Health Agency warehouse, 2 drugstore personnels, 1 person in charge of hospital warehouse, 5 persons in charge of public health centre warehouse, 1 on duty midwife in hospital, 2 on duty midwives in public health centre, 15 on duty midwives in assigning public health centre, 1 on duty midwife in childbirth clinic, and 4 independent-practice midwives.

Interviews were conducted by two skilled and experienced personnels in qualitative study. In-depth interviews were conducted for 25-45 minutes, both face-to-face interviews at home or in participants' work offices as required by participants, and telephone calls. The results of interviews were then processed and verified. Data verification was carried out by doing an abrupt supervision in the oxytocin storages to examine the justified information given by the participants concerning orders, storage, distribution and application of oxytocin as well as collecting proofs such as photos of oxytocin storages in the field.

To generalize the findings, data analysis of interviews was made in the form of questionaires and they were distributed to the medicine suppliers, persons in charge of the medicine, and health personnels in the area of Indragiri Hilir Regency. The filled in questionaires were then verified to make sure that the participants gave the justified data. Out of 165 questionaires which were distributed, 123 were well verified. The data was then processed univariatably and presented in the form of frequency distribution as shown in table 1, 2 and 3.

RESULT

Since 2003, the use of oxytocin as an optional uterotonic medicine on active management of third stage of labour has become an obligatory protocol in normal childbirth in Indonesia. From the confirmed data by Indragiri Hilir District Health Office in 2016, there was 10,979 childbirths provided by health providers. All of the childbirths have used oxytocin in active management of third stage of labour.

Medicine supplier: This study found that the agencies or organizations which provided all health services in Indragiri Hilir Regency with this medicine was the Regency Health Agency and drugstores which were directly supplied by medicine manufacturers or Limited Companies operating out of the regency. The delivery process was done on land transportation, with various delivery time of less than 12 hours to more than 2 days. Some agencies used cooler boxes to deliver the medicine, and some other did not. The medicine, which was delivered using cooler box, was first packed in aluminium foil and then it was put in a cooler box with some ice gel pack inside. It was difficult to mantain cold chain in a long delivery trip, meanwhile the temperature in the car was hotter and damper since it was caused by the effect of the car hot engine. Orders of medicine were done once a year but orders from drugstores depended on the minimum stock which should be available in each drugstore. After arrival, some medicines were put in the cooler chest, but some were only kept in the medical chest without any cooler equipment. Electricity in the supplier was on for 24 hours. Out of 11 medicine suppliers in the area of Indragiri Hilir, 6 were identified with participant characteristic as shown in medicine supplier table 1.

"*we have made efforts to maintain cold chain by packing the medicine in aluminium foil, then we put it in the cooler box with ice gel pack inside*" (participant 7).

Table 1. Medicine suppliers (n=6)

Characteristics	n (%)
Group of medicine suppliers	
Health agency	1 (17.0)
Drugstores	5 (83.0)
Source of medicine	
Medicine manufacturer	5 (83.0)
Limited company	1 (17.0)
Medicine delivery from place of source	
Land transportation	6 (100.0)
Water transportation	0 (0.0)
Duration of delivery from the source to the supplier	
≤12 hours	1 (17.0)
1 day	0 (0.0)
2 days	3 (50.0)
>2 days	2 (33.0)
Handling of medicine	
Cooler box	3 (50.0)
Non-cooler box	3 (50.0)
Purchase of oxytocin	
Annually	1 (17.0)
Depending on needs	5 (83.0)
Medicine storage in the supplier	
Special cooler	3 (50.0)
Medicine chest	3 (50.0)
Electricity in the supplier	
On for 24 hours	6 (100.0)
On for 12 hours	0 (0.0)

Medicine Warehouse: It is a place for receiving and storing medicine before being distributed to the health service centres in the area of Indragiri Hilir. Medicine

warehouses in this area include hospital and public health centre's medicine warehouses. Hospital medicine warehouses receive the medicine directly from limited companies located outside the regency, but public health centre medicine warehouses get the medicine from the Regency Health Agency.

Table 2. Medicine warehouse (n=15)

Characteristics	n (%)
Group of medicine warehouse	
Hospital	2 (13.0)
Public health centre	13 (87.0)
Source of medicine	
Limited company	2 (13.0)
Health agency	13 (87.0)
Delivery of medicine from medicine supplier	
Land transportation	7 (47.0)
Water transportation	8 (53.0)
Duration of delivery from supplier to medicine warehouse	
2-4 hours	12 (80.0)
1 day	2 (13.0)
2 days	1 (6.7)
Handling of medicine	
Cooler box or medicine thermos bottle	9 (60.0)
Non-cooler box	6 (40.0)
Order of medicine	
Annually	1 (6.7)
3 Months	12 (80.0)
Monthly	0 (0.0)
Depending on needs	2 (13.0)
Trade mark of medicine	
Oxytocin	15 (100.0)
Pitogin	0 (0.0)
Syntocinon	0 (0.0)
Storage in the warehouse	
Special cooler equipment	3 (20.0)
Refrigerator	5 (33.0)
Medicine chest	7 (47.0)
Drug display case	0 (0.0)
Electricity in the medicine warehouse	
On for 24 hours	9 (60.0)
On for 12 hours	0 (0.0)
On only in the morning	0 (0.0)
On only in the afternoon	0 (0.0)
On only in the evening	0 (0.0)
On only at night	6 (40.0)
Duration of storage before being distributed	
Monthly	11 (73.0)
Weekly	0 (0.0)
Depending on needs	4 (27.0)

Most of the area are parted by rivers, therefore delivery of medicine from the medicine sources to the medicine warehouses are done by way of water transportation, however some deliveries are done by way of land transportation which take 2-4 hours until 2 days. Oxytocin delivery processes from the medicine sources to the medicine warehouses usually use cooler boxes, but some are delivered without cooler boxes. Orders of oxytocin by hospital warehouses are done annually, meanwhile orders of oxytocin from public health centres are done every 3 months, monthly and depending on the needs. Oxytocin is the trade mark of the medicine which is provided both by Regency Health Agency and limited companies. After oxytocin is received by the person in charge of the warehouse, the medicine is then stored in a special cooler equipment or in a simple refrigerator, or in a medicine chest where the room temperature is >30^{o}C. Electricity in some medicine warehouses is on for 24 hours, but electricity in some other warehouse is only on at night. 15 out of 28 questionaires for medicine warehouses were already filled in and were verified to examine the justification as shown in the description of medicine warehouse table 2.

"*I know that the medicine cold chain should be well maintained, but there is no proper cooler equipment both portable and non-portable in this place. I have proposed it but it is not that easy to make it come true"* (participant 5).

Health Service Centre: Health service centres that help childbirth in this area include hospitals and public health centres, assigning public health centres, childbirth clinics, and independent-practice midwives. The hospitals receive medicine from hospital warehouses, and public health centres and assigning public health centres get medicine from public health centre warehouses, while childbirth clinics and independent-practice midwives buy medicine from drugstores. Like the medicine warehouse, delivery of medicine from the sources to the health service centres is done on land transportation, water transportation, or both, which take less than 15 minutes to more than one day. Generally, delivery to the assigning public health centres takes longer time since they have to cross rivers[19]. Frequently, the personnels have to spend the night in the place of source because they can not get *pompong* (small boat) to take them back at the same day. Participants revealed that they brought medicine in a simple medicine thermos bottle, but some only put the medicine in a plastic bag. Order of medicine is done every 3 months, or depending on the needs of hospitals and public health centres, because the distance between health service centres and medicine warehouses is near so that order of medicine depends on the needs. The trade marks of medicine which are available in health service centre are oxytocin, pitogin, and syntocinon[20]. The medicine received is then stored in the storage places such as simple refrigerator, drug display case with no cooler equipment, small plastic locker with no cooler equipment or they just put it in a small bowl. The medicine is stored in a simple refrigerator together with other medicines, but sometimes it is stored with foods and drinks so that the frequency of opening and closing the refrigerator may be more than 10 times in one work shift. Electricity in some places of the area may be on for 24 hours, but more places only enjoy the electricity at night, even some places rely on solar energy so that there is no available electricity during the rainy season[19]. At the time of childbirth, the medicine is taken out of its storage place and it is absorbed, which may take less than 1 hour, 1-2 hours, or more than 2 hours. After arrival, the medicine is injected to the patient but in more cases, first it is put in an instrument basin. The description of health service centres can be seen clearly in table 3.

"*it takes 4 hours using a boat from the assigning public health centre to the public health centre medicine warehouse. Because of the long distance and sometimes there is no available boat, the moment is frequently made use by the health personnels for visiting their relative's*

houses and more often they spend the night there" (participant 10).

"*I usually buy the medicine in a drugstore, and the medicine is not in a colling condition at the time of buying. The medicine is put into a plastic bag, and I store the medicine in the drug display case after arriving in the health service centre*" (participant 8).

Table 3. Health service centres (n=102)

Characteristics	n (%)
Health service centres	
Hospital childbirth room	2 (2.0)
Public health centre childbirth room	5 (4.9)
Assigning public health centre	78 (76.5)
Childbirth clinic	4 (3.9)
Independent-practice midwife	13 (12.7)
Source of medicine	
Hospital warehouse	2 (2.0)
Public health center warehouse	83 (81.4)
Drugstore	17 (16.7)
Delivery of medicine from the medicine source	
Land transportation	64 (62.7)
Water transportation	38 (37.3)
Duration of delivery from warehouse	
≤15 minutes	5 (4.9)
>15 minutes -1 hour	18 (17.6)
>1-2 hours	24 (23.5)
>2-12 hours	44 (43.1)
>12-24 hours	6 (5.9)
>1 day	5 (4.9)
Handling of medicine	
Cooler box or medicine thermos bottle	22 (21.6)
Non-cooler box	80 (78.4)
Order of medicine	
Every 3 months	73 (71.6)
Monthly	0 (0.0)
Depending on needs	29 (28.4)
Trade mark of medicine	
Oxytocin	88 (86.3)
Pitogin	13 (12.7)
Syntocinon	1 (1.0)
Storage place	
Special cooler equipment	0 (0.0)
Refrigerator*	11 (10.8)
Drug display case	74 (72.5)
Small plastic locker	6 (5.9)
Bowl	11 (10.8)
***Contents of drug storage place (n=11)**	
Special for medicines	6 (5.9)
Mixed with foods and drinks	5 (4.9)
) Frequency of opening and closing storage place (n=11)	
Depending on number of childbirth	5 (4.9)
>10 times in each work shift	6 (5.9)
Condition of electricity	
On for 24 hours	33 (32.4)
On for 12 hours	0 (0.0)
On only in the morning	0 (0.0)
On only in the afternoon	4 (3.9)
On only in the evening	0 (0.0)
On only at night	60 (58.8)
Rely on solar energy	5 (4.9)
Length of time after being taken out of the storage and before being administered	
<1 hour	9 (8.8)
1-2 hours	77 (75.5)
>2 hours	16 (15.7)
Places to put medicine after being absorbed	
Directly injected to the patient	11 (10.8)
Instrument basin	91 (89.2)

DISCUSSION

According to the findings of this study, efforts had been made to maintain cold chain during delivery process of the medicine to the suppliers (50%), medicine warehouses (60%) and health service centres (22%) using conventional non-electrical cooler boxes, but the long distance and the hot temperature in the car prevented the medicine temperature from reaching 2°C to 8ºC. Although efforts had been made to maintain cold chain during delivery process, most health service centres (80.2%) stored the oxytocin in places which had no cooler equipment, including putting the medicine in a drug display case (72.5%), small locker (5.9%) and bowl (10.8%). Then, the health personnel took the oxytocin out of its storage place 1-2 hours (75.5%) and >2 hours (15.7%) prior to be injected to the patient. Other findings of this study revealed that some participants bought the medicine from drugstores in a condition where the cold chain was not well maintained. It was in accordance with the study by Stanton et al[21] where the sold oxytocin ampul was put into a plastic bag with codes informing the date of purchase, date of expire on ampul, place of selling, and name of the area. Oxytocin in the plastic bag was then stored in a place with cold chain management and it was put in a cool room or in a local hospital cooler equipment as soon as possible. Different things were found in this study where the oxytocin bought in a non cooling condition was then stored in non-cooling places. The findings of this study indicated that there was a violation on oxytocin cold chain in this peripheral area.

Cold chain is a regulating system related to logistic to guarantee that oxytocin is always in a temperature of 2°C to 8°C during process of storage, handling, transporting, and distributing the medicine[14]. It is of vital importance to comprehend the purpose of fixing the date of expire by pharmacy industry. Fixing the standard and specification of medicine is meant to maintain the effectiveness and clinical safety so that it can provide the society with optimal health benefit. Fixing the standard of medicine storage by pharmacy industry is generally determined from the test results which are based on study of accelerating stability, in which products are stored in an accelerating condition (more extreme) for a long period of time (for example 6 months). The estimation of time based on the data is then used as a basic pre-determination of product storage time[11]. In this case, comprehension of medicine characteristics becomes very important because the medicine stability depends on many factors, including active materials, solvent (excipients), product form, process of manufacturing and its packing characteristic[22,23]. Connors, et al[24] also revealed that the effectiveness of products might decline after a long time because the active material was also declining, and potential loss of medicine was usually a result of chemical changes. The medicine characteristics may change in different levels, depending on the temperature and duration of exposure to the temperature. Cold chain may be damaged in an

unexpected way during daily practice. The damage can be caused by electrical power failure, broken cold storage room, improper transportation or failure of storage condition. This may not only affect some medicine units in hospital's treatment rooms, but also affect its whole clinical places[14]. Two main aspects of the medicine quality control which are frequently reported in studies of medicine quality are Active Pharmacological Ingredient (API) and sterility which is an important attribute of less heat-proof injection medicine (thermolabile). Oxytocin has a molecular formula of $C_{43}H_{66}N_{12}O_{12}S_2$[25]. According to Farmakope International, medicine has to contain oxytocin not less than 90% and no more than 110% as listed in the label and it must be sterile. Products containing oxytocin less than 90% or more than 110% are considered non-standardized and should not be used in medical treatment. This limitation is also used by British Pharmacopoeia and US Pharmacopeia[15].

Oxytocin has storage time duration of 3 years when it is stored in temperature of 2°C to 8°C[6] and it can be safely stored for 3 months in temperature of 30ºC[12,13] meanwhile Parraga et al. revealed that oxytocin was stabile for ≥1 month (28 days) in temperature of 25°C[14] and Hogerzeil et al. reported that short period of transportation without cooler equipment for no more than 1 month in temperature of 30°C or 2 weeks in temperature of 40°C was still tolerable. However, for oxytocin which was stored constantly in temperature of 30°C, the potential would decline 14% after 1 year. Meanwhile, continuous temperature exposure reached 40°C might cause declining potential of 6% for more than 1 month and might reach 50% after 1 year[6]. Study by WHO also found that oxytocin did not lose its active material after 12 months storage in temperature of (4°C to 8ºC), but oxytocin lost 3%-7% of its active material after 12 months storage in temperature of 21°C to 25ºC, lost 9%-19% its active material after 12 months storage in temperature of 30ºC, and it has no effect when exposed to the light[6]. It can be concluded that lower level of active material in oxytocin ampul has nothing to do with date of expire but it is caused by the declining potential of medicine[21].

Many previous studies have proven that heat exposure to oxytocin is so far still tolerable. However, the problem is the difficulty to determine how much heat exposure which is already received and how long heat exposure which has been lasting to the oxytocin, starting from the medicine producers to the application to the patients. Analysis of mother's mortality related to the use of oxytocin, where the policy of using oxytocin is considered as an optional uterotonic medicine in active management of third stage of labour, has long been applied to prevent and handle postpartum haemorrhage. Even up to now, oxytocin has been applied in almost all childbirth process as reported in the findings of this study. However, cases of postpartum haemorrhage are still in the first level. In Indonesia, the use of oxytocin has become a compulsory protocol in the third stage of labour. This has been applied since 2003 and based on health demography survey in 2012, 83% of childbirths in Indonesia have provided by health providers where all childbirths have used oxytocin as an optional uterotonic medicine in active management of third stage of labour, but the maternal mortality rate is rising compared to five years before, that was 228 out of every 100.000 successful childbirth in 2007, then it was rising to 359 out of every 100.000 successful childbirth in 2012 with the haemorrhage case percentage of 42%[26]. How is the oxytocin quality in the field? And how effective oxytocin is to prevent and handle bleeding cases? Problems of cold chain and low quality of oxytocin are not only found in Indonesia but also in countries with low–medium income per capita, especially in Africa and Asia. This has become a potential factor that causes high level of pain and maternal mortality[15]. Anxiety on the effectivity of oxytocin to prevent postpartum haemorrhage in tropical areas with coller storage equipment is not unreasonable[27]. Results of studies in India reported that 33%-40% oxytocin ampul in Karnataka and 22%-50% in Uttar Pradesh had non-standardized specifications, and the two areas stored more uterotonic medicines without cooler equipment[28]. Some studies in Indonesia also reported that a small number of oxytocin samples had API <90% (8 out of 13 samples) and >110% (3 samples). Some surprising findings in Ghana reported that 65.5% oxytocin available in Ghananian market did not meet the standard, even some medicines from some manufacturers were indicated fake medicines[29]. The needs of high quality uterotonic medicine to prevent and handle postpartum haemorrhage in poor countries are undeniable. The best practice for a long storage of all uterotonic injections is cooler equipment[21].

Besides, justification for violation of cold chain is a big problem and dangerous because it can make health personnels neglect their responsibilty. The same thing was also revealed by Hodgins[11], When standard and specification are considered arbitrarily, and do not represent performance and actual product safety, it can encourage health personnels to neglect storage norms and date of expire, which is an example of dangerous manners and attitude. Although violation of oxytocin cold chain is still tolerable for the time being, most studies reported that oxytocin cold chain would have an effect of potential decline constantly from time to time and made oxytocin less effective before its date of expire[9,11,21,30]. When safe storage of oxytocin is not tightly applied, the criteria of cold chain storage become an objectionable requirement. Therefore, pharmacy industry needs to examine again the storage time and storage specification (including temperature requirement) in order to optimize the effectiveness, safety, and product accessibility[11]. Only when there is confirmation from pharmacy industry on parameter and stability of oxytocin should the cold chain be maintained in accordance with storage directions attached on the lable of oxytocin[31].

CONCLUSION

Most of the cold chain of oxytocin is not maintained from drug suppliers, drug warehouses, health care providers to the patients. In order to provide the society with optimum health benefit, intolerable violation of oxytocin cold chain should not be used as a justification, except that there is a confirmation of new parameter from the pharmacy industry related to the oxytocin stability. There is a consequence of oxytocin potential decline for every violation. Next studies need to examine oxytocin quality in the peripheral area to make sure that the medicine is effective to prevent and

handle postpartum haemorrhage. The government should examine unregistered and below standard medicine manufactures, and encourage law enforcement for every violation.

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