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Review Article

Impact of Oxytocin Administration on Milk Quality, Reproductive Performance and Residual Effects in Dairy Animals – A Review

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Abstract | Posterior pituitary releases a hormone named oxytocin (OT) that causes contraction of smaller ducts and myoepithelial cells surrounding the alveoli of mammary glands. The milking process is allowed to be managed by an exogenous OT by its vital role in neuro hormonal milk-ejection process. OT increases milk yield by ↑ gland output, which is not due to residual milk removal. OT also improves the persistency of lactation. Receptor blockade of oxytocin causes milk ejection inhibition. OT injections cause increased OT blood levels which results in the prolonged myoepithelial and alveolar contractions that ultimately increase milk yield. Milk composition especially protein, fat, lactose and mineral concentration are influenced by exogenous OT administration. It affects the cell maintenance and mammary metabolism along with its proven physiological role in the milk ejection reflex. OT effects are not manifested through effects on cell remodeling. Observed effects of OT administration on reproductive anomalies are anestrous, the development of corpus-luteum cysts, follicular ovarian cysts, delayed age at puberty, repeated estrous cycles, dystocia, abortions, dead fetuses and retention of the fetal membranes. OT administered exogenously or secreted endogenously, establishes in minutes the desired effects and metabolized to inactive products rapidly in the body. Irrespective of whether OT is ingested with milk or secreted into the milk, it is degraded readily by gut-enzymes so that it doesn't reach the circulation in biologically-active form so there seems to be less or no harm in consumption of milk from OT-treated-animals. But OT has remarkable effects on milk quality, composition and reproductive health of the dairy animals so it's use in dairy industry should be discouraged.

Novelty Statement | This literature meta-analysis is important to understand the disadvantages of exogenous use of oxytocin (OT) in milk industry. It is a sort of first study which will give a clear picture about OT administration and its residual effects. After reading this paper, one could know better about this malpractice.

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Introduction

Oxytocin means quick birth; a word which is derived from Greek. It is a peptide hormone synthesized in magnocellular-neuro-secretory-cells in supraoptic and para ventricular hypothalamic nuclei while stored in posterior pituitary lobe then released in the blood as a result of a neuroendocrine reflex. OT is packaged in granules, then transported-down with posterior- pituitary-gland-axon and excreted to the systemic circulation with carrier protein, the neurophysins. It is related to the reproductive

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process causing the womb to contract. Similarly, an estrogen dominated myometrium such as is found at ovulation and at parturition, seems more responsive to OT, and as a result it causes greater contraction of the uterus. Release of OT at that time is associated with subsequent myometrial contractions and appropriate stimuli that assist the transportation of sperm to the oviduct at copulation and helps in the expulsion of the fetus at parturition; hence plays important role in completion of the fertilization process. OT is also secreted into the blood in both females and males also at the sexual orgasm. In cow/buffalo OT is secreted in brain and few other tissues along with ovaries, testes and corpusluteum (Wathes *et al*., 1983).

In all the mammals OT is secreted endogenously for induction and maintenance of labor at birth process and for milk letdown in lactation. It causes uterine contraction as well as milk-ejection through promotion of myoepithelial-cell's contraction which surrounds milk alveolus. Natural OT causes milk to be ejected from the breasts during lactation: the amount of OT produced naturally, however, does not stimulate labor. For induction of labor at birth there is a need for administration of exogenous oxytocin. In order to duplicate the hormone and create an artificial drug OT (Syntocinon) was developed in 1953 by Vincent du Vigneaud (Bruckmaier, 2003). In case of the non-progression of parturition, generic oxytocin analogues (synthetic OT) are used to facilitate the birth by induction and support of labor. It is very important physiologically for cervical dilation before the birth and contractions in 2nd and 3rd stage of labor during delivery process.

The half-life of the OT in blood is 0.55 to 3.6 minutes, so it rapidly disappears from blood stream through the action of various enzymes only within 2-6 minutes (Ijaz and Aleem, 2006). OT causes contractions of the smaller ducts and myoepithelial-cells around the alveoli of mammary gland. After discovery of OT and studying it's role in neuro-hormonal-milk-ejection process, it was recognized as a pharmacologic agent to facilitate and allowed the managing of milking-process with an exogenous-OT administration; Thus it ↑ the yield of milk in dairy animals (Kiran, 2001).

OT Applications

The synthetic OT is used in veterinary and human medicine practice. OT is the drug of choice to augment and induce the rhythmic contractions of the uterus during the desultory labor both in human and veterinary treatment. It is used to prevent and control the bleeding after abortion and childbirth. It is also used for the management of inevitable abortions and for the induction of abortions therapeutically. Clinical use of OT for promotion of the milk-ejection in lactating women which experience breast feeding difficulty is also equally important. Moreover, it is used for the treatment of cases like breast engorgement and mastitis. OT is used universally for expulsion of retained placenta after delivery and to induce the letdown of milk in veterinary practice. OT is also used to aid the delivery when female has been in labor for an extended period in young animals.

Furthermore, OT is also very helpful in the management of post parturient uterine prolapse. It is employed frequently as an adjunct to the antibiotic-therapy for the treatment of mastitis in lactating animals (Ijaz and Aleem, 2006). It is often administered in dairy practice to reverse any failure in milk ejection caused by a lack or reduction in endogenous OT release. It is also administered in the cases of agalactia. However, the effect of its injection on milk ejection efficiency and blood flow pattern is unclear. Although genetics, hormonal status, environment, milking frequency and nutritional status are the main factors which regulate the milk yield in dairy animals (Bruckmaier, 2003; Lollivier *et al*., 2005). In addition, long term treatment of OT in cows reduces the spontaneous milk-ejection upon cessation of the treatment. Meyerhoff (2016) reported that in dairy farming exogenous administration of OT helps to release milk by simultaneously stimulating and calming the animal. So, it is very useful to the farmer if the animal is stressed-: examples include when animals are milked for the first time or experience a difficult birth. In the uterus OT plays its role by binding to specific receptors which are present on smooth muscle cells. At the point of parturition or when babies are delivered prematurely, the number and affinity of OT receptors increases. During fetal expulsion OT is secreted by the posterior pituitary and by intrauterine tissues in a pulsatile manner. While in mammary tissues myoepithelial cells have OT receptors which performs bindings, contract in response to their activation by OT resulting in ejection of milk from milk ducts (Rogers, 2016).

Effects on milk production

OT administration to cattle for whole lactation resulted in ↑ milk yield by 11.6% over control animals (Nostrand *et al*., 1991). Similarly, milk production ↑ ($P<0.05$) through the use of oxytocin treatments (Bencini *et al*., 1992). Ballou *et al*. (1993) found that OT increased ($P<0.05$) milk production by 3% before and after milking which is increased gland milk output rather than residual milk removal. It is obvious that total evacuation of the udder during milking so that there is no-residual milk reduced production-losses which occur when using once a day milking, while ↑ the rate of milking was found ineffective in reduction of losses (Carruthers *et al*., 1993). Bruckmaier *et al*. (1994) noted that in goats prestimulation of the mammary gland caused the release of sufficient OT to release the large volume of cisternal milk present without causing the characteristic bimodal pattern of milk flow. Moreover milk-ejection in ewes also occurred in response to higher OT concentration (Bruckmaier *et al*.,

1997a) which need to be sustained to maintain mik let-down over the entire milking (Bruckmaier *et al*., 1997b; Bruckmaier and Blum, 1998). Furthermore, exogenous OT injections at non-milking times ↑ the milk yield and improved glactopoiesis in the ewes (Zamiri *et al*., 2001). Thus, OT influences cell maintenance and mammary metabolism in addition to its traditional role of facilitating milk let-down (Bruckmaier, 2003). The use of OT to promote milk letdown, in particular when the glands are engorged with milk, can prevent udder damage and promote udder health.

Machine milking necessitates the separation of cows from their calves and under these conditions, there is a transient ↓ in OT release, milk production and flowrate (Tancin *et al*., 1995). With machine milking the pattern of milk let-down is different however milk yield is not significantly affected (Bruckmaier *et al*., 1996). For all the milking frequencies, the initiation of milking is followed by significant ↑ in circulating OT levels. Increase in milking frequency each day augments the milk yield while a ↓ in frequency reduces the yield while also changing milk composition (Negrao *et al*., 2001; Lollivier *et al*., 2002). According to the narrations of Weiss *et al*. (2003) milk production is ↑ in hand-milking/suckling than machine-milking as ↑ OT levels are synthesized and released. Dzidic *et al*. (2004) studied single stall automatic milking systems while monitoring milk ejection, OT release and milking characteristics and identified that OT levels didn't differ between treatment groups after the initiation and throughout of milking process. On the other hand, the sensitivity of mammary glands to the actions of OT was reduced in response to chronic OT treatments since there was a reduction in the contractibility of the myoepithelial cells under normal physiological OT concentrations. Thus, the OT effect or pathway became desensitized resulting in prolonged myoepithelial/alveolar contractions (Macuhova *et al*., 2004).

Thomas *et al*. (2005) found an ↑ in milk yield with OT administration and reported a positive correlation between the total time OT concentrations exceeded threshold levels and milk yield harvested by machine. Lollivier *et al*. (2005) confirmed the galactopoietic effect of OT and reported that additional milking increased milk yield by 8% and milk constituents by 6%. In addition to this, Passille *et al*. (2008) noted that residual milk production was ↑ in nursing cows than control cows, respectively (8.7±0.8: 3.2±0.8 kg) after the injection of OT. In Pakistan Akhtar *et al*. (2012) investigated the effects of OT administration before milking on milk yield in Nili-Ravi buffalo and found a significant increase in milk yield over the control group. While working on a project about poverty alleviation and rural development by livestock extension education in southern Punjab, author observed that mostly people use exogenous OT injection for the letdown of milk in animals especially in buffaloes and they reported that by the use of OT injection the amount of milk produced has been increased (Faraz *et al*., 2019). Administration of exogenous OT gave a similar response ($P<0.05$) in polish red cows Dymnicki *et al*. (2013).

Effects on milk composition

OT administration does not affect the percentages of milk fat, lactose, protein, somatic-cell counts (SCC) or milk plasmin activity (Nostrand *et al*., 1991; Bencini *et al*., 1992). Ballou *et al*. (1993) reported that the effects of OT are not manifested through changes in cell remodeling. In contrast to that, there was significant decrease in percent acidity, protein, fat, solids-not-fat (SNF) and total-solids of OT injected milk in buffaloes as reported by Kiran (2001). This response may be due to variations in diet, season, the timing and dose of exogenous OT injections. On the other hand, Indian scientists Sing and Aggarwal (2001) studied the mineral composition in milk of Murrah buffaloes as affected by exogenous OT administration and found that Cu, Mg, Zn, Fe and Mn secretion is influenced by OT administration as increasing Cu and Mn contents while decreasing Mg, Fe and Zn contents; however, Ca secretion is not affected. In another study Lollivier *et al*. (2005) determined that fat and protein were positively correlated; when one decreased the other one also decreased with, SNF and total solids contents following the same pattern. However, there was also significant decrease in copper and iron concentrations. In general most studies report that OT injections have no effect on milk trace element concentrations and their deficiency can be attributed to an imbalanced diet offered to the animals. Chronic OT administration has also been shown to increase electrical conductivity and SCC of milk as well as lactose and K levels in the systemic circulation (Misof *et al*., 2007).

In Pakistan increases in Na, Cl, Cu and ash contents and decreases in lactose and K contents were observed in OT administered Sahiwal cows (Hameed *et al*., 2010). While Akhtar *et al*. (2012) investigated the effects of OT administration before milking on SCC and fat content in milk of Nili-Ravi buffalo and found that SCC was increased by OT injection whereas there was no effect on milk-fat %. On the other hand, Dymnicki *et al*. (2013) evaluated effect of OT injections on composition of milk in Polish red cows and concluded that administration of OT increased ($P<0.05$) milk fat percentage.

Effects on reproductive health

The use of exogenous OT at milking increased lactation milk yield with no apparent effect on reproductive health (Nostrand *et al*., 1991). Milk letdown without administration of OT seems to be difficult in the animals which regularly exposed to OT injections as they become habitual to the drug. While repeated administration of OT injections therefore interferes with the normal

mammary epithelium milk secretary activity thus inhibits the normal milk ejection process and affect reproductive health (Mustafa *et al.*, 2008).

It is believed that the prolonged use of OT injections also causes fertility disorders like poor estrus signs, reduced lactation period, lower conception rate and high embryonic mortalities in the local herds of cattle and buffalo (Siddiqui and Saeed, 2000). Delayed puberty, lower conception rates, increased abortion rates, lower pregnancy chances, delays in the duration of placenta expulsion, ovulation interval, shortened postpartum estrus interval and calf death soon after the delivery because of poor quantity and quality of milk have also been observed (McDonald, 1989; Bhullar *et al.*, 1991; Dominguez *et al.*, 1993; Weiss *et al.*, 2002; Dzidic *et al.*, 2004; Mustafa *et al.*, 2008; Qureshi *et al.*, 2008). Further complications have been observed with OT treatment including delayed age at puberty, dystocia (difficult birth, abortions, dead fetus, retention of placental membranes, lower milk fat percentage and decreased milk production in buffalo and cows (Shaw, 1942; Hassan, 1993; Murugaiyal *et al.*, 2001; Weiss *et al.*, 2003; Thomas *et al.*, 2004; Ariota *et al.*, 2007; Bidarimath and Aggarwal, 2007; Qureshi *et al.*, 2008).

Reproductive anomalies such as ovarian follicular cysts, corpusluteum cysts, placental retention, anestrous and the repeated estrus cycles in cattle and buffalo have also been reported (Cameron and Fosgate, 1964; Labhsetwar *et al.*, 1964; Booth and McDonald, 1982; Peters and Laven, 1996; Tiwari *et al.*, 1999; Mavi *et al.*, 2004; Drillich *et al.*, 2006, 2007). OT affects the cell maintenance and mammary metabolism in addition to its well-established physiological role in the milk-ejection reflex (Zamiri *et al.*, 2001). There seems to be no harm in humans consuming the milk from OT treated animals. However, its usage in the pregnant dairy animals should be discouraged (Ijaz and Aleem, 2006). Iqbal *et al.* (2013) studied OT induced oxidative stress in lactating Nili Ravi buffaloes and reported that OT injection resulted in an ↑ oxidative stress by increased ceruplasmin and total homocysteine oxidase activity and ↓ the enzymatic activities of antioxidant enzymes including arylesterase and paraoxonase-1- Their changes are very likely to reduce the reproductive and productive performance of buffalo.

OT administration directly affects the bovine reproductive system thus reducing the life expectancy of animal as reported from India (Naidu, 2013). Moreover, Gupta (2014) reported on the use of OT in the dairy industry, suggesting that its uncontrolled use for milk let-down should be illegal. His conclusion was based on the hormonal imbalance and harm to the reproductive system of treated animals, thus reducing their lifespan. A similar conclusion was drawn by. G.N. Singh after studying its use on small-holder dairy farms in India (Sharma, 2015). Anjali Aggarwal reported the perception that OT injections for milk let-down in pregnant animals may cause abortion is incorrect, as OT receptors remain absent throughout gestation and appear only towards the end of pregnancy. She also added that OT has a short life span of about 2-2.5 minutes so that side effects on animal health are likely to be minimal. In same report, Srivastava stated that lack of response to normal stimuli for milk ejection and addiction in animals are the main disadvantages of continuous usage of OT injections (Arora, 2016). In Pakistan, working on a project "*Setting-up livestock farmer's data base in Southern Punjab*", Faraz and Waheed (2020) observed that people mainly use OT for milk letdown in their animals and they reported that by using OT injections, the animals may get problems of abortion, mastitis and metritis (*Personal Communication*).

In Pakistan, the use of exogenous OT extensively for milk letdown is widespread on small-holder dairy operations. No doubt it is a malpractice that definitely disrupts the normal natural milk ejection process and has an adverse effect on reproductive health in dairy animals. Milk quality is also affected by OT administration in dairy animals. Farmers commonly use this hormone for milk letdown as it is easily available at retail shops in our country. The dose used by farmers are not regulated and so the use of this drug is based on the farmer's own experience without any knowledge of the side-effects of the drug on reproductive health and milk quality. Clearly the education of farmers on OT use is lacking in this area across Pakistan.

Residual effects

Ballou *et al.* (1993) reported that the effects of oxytocin administration are not manifested through effects on cell remodeling. It is a peptide hormone which is synthesized in hypothalamic neurons and then released from posterior pituitary lobe. OT produces its desired effects in minutes and then is readily metabolized in inactive products. It is mostly secreted and ingested along with the milk, it is efficiently degraded by gut enzymes so can't reach the blood circulation in biologically active form (Ijaz and Aleem, 2006).

Pullakhandam *et al.* (2014) determined that oxytocin injection in milking buffaloes do not influence the content of OT in milk. OT that is found in milk, is rapidly degraded during intestinal digestion, and so is not absorbed intact to pass via the circulation to accumulate in milk or meat: thus, there are no harmful side effects for humans consuming these products. (Meyerhoffs, 2016). However, in another study from India, consumption of milk from OT injected animals can cause hormone imbalances in some humans leading to health problems (Naidu, 2013).

Conclusions

The benefits and safety dosage for OT administration at different concentrations in dairy animals is not thoroughly understood yet. It is obvious that OT does have significant effects on milk composition and also affects the reproductive health of animals. However, there seems to be no effects on consumption of milk sourced from OT treated animals. Its indiscriminate use for milk letdown should be discouraged and awareness among farmers should be created. This education process is necessary, so that the dairy industry of Pakistan can flourish and produce milk of a high enough quality to meet international standards and to compete successfully in the world export marketplace.

Conflict of interest

The authors have declared no conflict of interest.

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