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Streptokinase Adverse Reactions: A Review of Iranian Literature

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ABSTRACT

Thrombolytic agents are among the medications that are used widely for the treatment of thromboembolic disorders and myocardial infarction (MI). Despite the world-wide availability of newer specific agents, streptokinase (SK) is still the most frequently used medication from this class in Iran. Hence we conducted this study to review the adverse reactions to this medication which were reported in the Iranian studies. We preformed this study by searching the English resources such as Pubmed, Google scholar and Scopus. Additionally, we searched Google scholar, Scientific Information Database, Magiran and IranMedex to cover Persian articles.

We found 50 articles from the mentioned resources after deleting the duplicated records. Nineteen articles remained after implementing the inclusion and exclusion criteria. In most of the studies the indication for SK treatment was MI. Assessment of streptokinase ADRs was the main focus of 7 studies. The most frequent adverse drug reaction (ADR) was related to the cardiovascular system. Among them arrhythmia and hypotension were the most frequent ones. The second most prevalent ADR was bleeding followed by allergic reactions. In two studies only a single system ADR was studied: neurologic adverse effects and elevation in liver enzymes. Only very limited number of studies assessed the causality of the ADRs which made the interpretation of the results difficult. Among the associated factors that were assessed as risk factors of ADRs, age was the focus of 2 studies. The Iranian studies reported frequent ADRs similar to previous reports. However, due to the heterogeneity of the studies we could not describe the frequency and severity of reported ADRs in a more clear and precise conclusion.

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Introduction

Cardiovascular diseases (CVDs) are the most significant health problems and the leading causes of mortality and morbidity in recent decades (1). In 2012, 17.3 million deaths occurred due to CVDs worldwide (2). Coronary artery disease which accounts for nearly one-third to one-half of all of the cases of CVDs (3) is reported to be one of the major causes of death in developing and middle east countries including Iran (4-5).

Several medications are used in the management of coronary artery diseases and acute coronary events (6). Thrombolytic agents are widely administered for the treatment of acute coronary events and other thromboembolic diseases (7). These agents are considered as the first line treatment option in many cases of acute myocardial infarction (AMI) (8).

Streptokinase (SK) is the first and leading thrombolytic agent entered the market and leading for the treatment of AMI and other thromboembolic conditions for more

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than 50 years (9-10). Among thrombolytics, this indirect fibrinolytic agent is the most commonly used and studied due to its availability and lower cost in comparison to other agents in this pharmacologic class (11).

Narrow therapeutic window and life threatening adverse reactions are major challenges of thrombolytic therapy (12). SK was reported to be one of the most frequent causes of adverse drug reactions (ADRs), among antithrombotic-thrombolytic medications in hospitals (13).

Different adverse reactions from SK have been reported ranging from minor and major bleeding to hypotension, arrhythmia and allergic reactions (8, 14). However, it has been proposed that the risk of debilitating and life threatening ADRs, such as cerebral hemorrhage, severe bleeding, severe hypotension and allergic reactions was relatively low (12). Incidence and severity of ADRs caused by SK might vary depending on the patients' clinical status, indication of treatment, dosing regimen and medication preparation and source of SK (6, 9, 15-20). However, it seems that no comprehensive review article describing ADRs of SK has been published.

For a long period, the only thrombolytic agent that was available in Iran was SK. Despite widespread use and availability of several studies that addressed the ADRs due to SK in Iran, as far as we know, there is no review article that mainly focused on the ADRs of this medication in our country. Therefore, we decided to review the available literature regarding ADRs caused by SK in Iran. In our opinion, it is also the first review article regarding SK ADRs in the Middle East and developing countries.

Methods

We conducted this review by searching English and Persian literature in which ADRs due to SK in Iran were reported. We performed search in the English resources including Pubmed, Google scholar and Scopus. To include Persian articles, we searched Google scholar, Scientific Information Database (SID), Magiran and IranMedex which together are covering a wide range of Persian articles. As the final step we did refernce tracking to find more relevant studies.

The mentioned resources were searched using the terms "streptokinase" and "Iran" in combination with one of the following phrases "adverse drug reaction", "adverse events", "side effect", "drug events", "adverse drug effect" and " Acute Myocardial Infarction (AMI)", in English and with Persian equivalents in appropriate resources.

Inclusion/Exclusion Criteria

We included all of the case reports, cross-sectional, case-control, clinical trial and cohort studies on adult and children in which they recieved SK and at least one adverse effect of SK was reported. We excluded letters, thesis, abstracts of seminars, book chapters, opinion papers as well as articles in any languages other than English or Persian.

Data Extraction

Two authors assessed these articles within title, abstracts and full texts regarding inclusion and exclusion criteria. Most of the considerable data of the finally remained articles were extracted in one table. We presented the study designs, number of patients, demographics of patients (age, sex), number of patients who experienced at least one ADR during the study, underlying disease, symptoms of ADRs, number of events, factors associated with ADRs whenever available and strategies to manage adverse effects. Severity, causality and/or preventability of ADRs were also mentioned if they were pointed out in the article.

Results

Our search in electronic resources yielded the following results 154, 79, 2, 69, 32 and 77 articles in Pubmed, Google scholar, Scopus, Magiran, SID and IranMedex respectively. Then, we manually tracked the references of the articles. After deleting the duplicated records, 50 articles remained. By implementing inclusion and exclusion criteria, 30 more articles were excluded. Among the remaining 20 articles, 11 were in Persian. Of nine English written articles, Feizi et al. study which, evaluated the clinical outcome of patients with ST elevation myocardial infarction (STEMI), was excluded during data extraction (21). This study compared the major adverse cardiac events in patients who received SK with those who did not receive within 30 days of MI. However, they did not clearly mention whether the events were attributed to SK or to the MI.

Among 19 articles, the relevant data of 14 of them was extracted and presented in Table 1 (1, 22-34). Remaining articles that could not be presented in the table because of heterogeneity of reported data were summarized and mentioned in the following parts (35-39).

Study characteristics

The most frequent designs of the articles were cross-sectional (prospective or retrospective) studies (11 articles) followed by quasi-experimental (4 articles), randomized clinical trial (RCT) (2 articles) and cohort study (1 article). Only one case report was found. All of the articles were published from 2001 onwards. The corresponding authors of the articles were physicians, pharmacists, nurses and microbiologist in 9, 5, 4 and one of the articles respectively.

Patients and SK indications

In 13 of the studies, the reason for administration of SK was AMI (22-26, 28-30, 33-35, 38-39). In two studies the indication of treatment with SK was thrombosis (27, 32). In the remaining four studies, the indication for SK

#	Author/ Year/ (Ref. N)	Study Design	Patients			ADR				
			N (F%: M%)	Age Y±SD (Range)	Disease	N patients (%)	N Events (%)	Associated Factors		Action Taken
								Significant	Non-significant	
1	Khani M, et al. 2001 (30)	Quasi-Experimental	**130** (29.2:70.8) SK+: 37 SK-: 93	58.2±11.7 62.2±12.9	AMI	-	SK+ vs. SK-[a] Cardiogenic shock (50 vs. 0)[b] Reinfarction (8.1 vs. 1.1) Angina after infarction (2.7 vs. 1.1) GI bleeding (2.7 vs. 0) ICH (2.7 vs. 1.1)	-	-	-
2	Nogh H. 2002 (26)	Quasi-Experimental	**68** SK+: 45 (40:60) SK-:23 (34.8:65.2)	**56±8**	AMI	-	SK+ vs. SK- (after 48 hrs)[c] ≥2*AST (48.8 vs. 8.7) ≥2*ALT (46.6 vs. 8.7) ≥3*AST (33.3 vs. 4.3) ≥2*ALT (33.3 vs. 4.3) ≥2-3*ALP (6.6 vs. 0)	-	-	-
3	Saffari M, et al. 2002 (25)	Cross-Sectional Prospective	**45** (27:73)	**65.4±10.5**	AMI	-	Hypotension (15.6) Cough (11.1) Bleeding (8.9) (3: IV Line site, 1: pulmonary tissue) Respiratory dispnea (8.9) Urticaria (4.4)	-	-	**DC**; Hypotension
4	Shemirani H. et al 2005 (23)	Cohort	**293** (26.6:73.4) Severe HTN (-) 161 Severe HTN (+) 132 [d]	**59.2±12.70**	STEMI	45 (15.35)	Hypotension 12 (4.1) Bradycardia 11(3.8) VT and VF 9 (3.1) Extracranial hemorrhage especially GI 8 (2.7) Ventricular septal defect 3 (1) Ischemic stroke 2 (0.7) ICH 2 (0.7)	-	Age Diabetes Mellitus IHD Smoking HTN Hyperlipidemia	-
5	Hakim SH, et al. 2006 (32)	Cross-Sectional Prospective	**17** (53:74)	**43.8±11**	Acute thrombosis of mechanical prosthetic valve	-	**Total 5** ICH 1 (5.9) Minor bleeding (Epistaxis, Hematuria) 2 (11.8) Systemic embolism 2 (11.8)	-	-	-
6	Noori N, et al. 2006 (27)	Quasi-Experimental	**33** (36.4:73.6)	**19.1±18.89** (month)	Children with femoral artery thrombosis after cardiac catheterization[e]	9 (27.5)	**Total 23** Local blood oozing 9 (27.5) Mild to moderate hematoma 8 (24.5) Bleeding 3 (9) Anaphylaxis3 (9)	**PT>13s;** In Hematoma	-	**DC**; Local blood oozing Hematoma **Symptomatic therapy**; Local blood oozing Anaphylaxis
7	Salarifar M, et al. 2008 (24)	Double Blind Randomized Clinical Trial	**221** Streptase® 102 (9.8:90.2) Heberkinasa® 119 (13.5:86.5)	56.9±11.1 57±10.6	AMI	95 (43) [i]	Streptase® vs. Heberkinasa® Bleeding 3 vs. 1 (2.9 vs. 0.8) Allergic reactions 14 vs. 20 (13.7 vs.16.8) Hypotension 20 vs. 26 (19.6 vs. 21.8) Arrhythmia 13 vs. 14 (12.7 vs. 11.8) Fever and chill 1 vs. 3 (1 vs. 2.5) HTN 3 vs. 0 (2.9 vs. 0) Respiratory Distress 1 vs. 0 (1 vs. 0) Cerebrovscular accident 1 vs.0 (1 vs. 0)	-	-	-

#	Author/ Year/ (Ref. N)	Study Design	Patients			ADR				
			N (F%: M%)	Age Y±SD (Range)	Disease	N patients (%)	N Events (%)	Associated Factors		Action Taken
								Significant	Non-significant	
8	Mohebbi N, et al. 2010 [i] (1)	Case-Series Prospective	**37** (-)	-	CVD	16 (59.26)	Serious ADRs: GI bleeding 1 (2.7) Hematemesis 1(2.7) Apnea bradycardia 1 (2.7) Apnea 1 (2.7)	-	-	**DC**; apnea **Symptomatic therapy** ; other serious ADRs
9	Nasiri M, et al. 2010 (28)	Quasi-Experimental	**60** [f] (18.3:81.7)	-	AMI	-	**Cardiovascular** [g] 43 (71.7) PVC 33 (55) PAC 1 (1.6) VT 10 (16.7) SB 2 (3.3) **Other** 11(18.3) N/V 1 (1.6) Fever and/or chills 8 (13.3) Bleeding 2 (3.3)	-	Age Gender History of MI History of chronic disease Chest pain severity	-
10	Shojaie M, et al. 2010 (22)	Cross-Sectional Prospective	**100** (18:82)	**61.7±11.7**	AMI	-	**Total 203** [h] **Cardiovascular** 154 (75.9) PVC 53 (26.1) VT 6 (2.9) VF 3 (1.5) SB 14 (6.9) AIVR 39 (19.2) AVB 9 (9) Hypotension 35 (4.4) **Bleeding** 26 (12.8) Mouth bleeding 12 (5.9) Subcutaneous bleeding 13 (6.4) ICH led to death 1 (0.5) **Allergic reactions** 23 (11.3) Chill 19 (9.3) Fever 4 (2)	**Age;** Hypotension and SB were higher in > 70 yrs	-	-
11	Karimzadeh I, et al. 2011 [i] (31)	Cross-Sectional Prospective	-	-	CVD	-	Hematuria 1 (-) GI bleeding 2 (led to death 1) (-) VT 2 (-) VF 2 (-)	-	-	-
12	Fayazi S, et al. 2012 (34)	Cross-Sectional Prospective	**120** (35:65)	20-80	AMI	-	**Total 90** **Cardiovascular** 40(44.4)**;** PVC 14(15.5) IVR 10(11) SB 4(4.4) AB 3(3.3) Hypotension 3(3.3) Flebit 3(3.3) VF 2(2.2) VT 1(1) **Bleeding** 21(23.3)**;** IV line site bleeding 6(6.6) Mouth bleeding 4(4.4) Subcutaneous bleeding 3(3.3) Hematuria 3(3.3) ICH 2(2.2) Epistaxis 2(2.2) GI bleeding 1(1) **Allergic reactions** 29(32.2)**;** Chill 9(10) N/V 8(8.8) Cough 4(4.4) Fever 3(3.3) Backache 2(2.2) Priorbital swelling 2(2.2) Bronchospasm 1(1) **Death** 6(5)	-	-	-

#	Author/ Year/ (Ref. N)	Study Design	Patients			ADR				Action Taken
			N (F%: M%)	Age Y±SD (Range)	Disease	N patients (%)	N Events (%)	Associated Factors		
								Significant	Non-significant	
13	Ghaffari S, et al. 2013 (33)	Double Blind Randomized Clinical Trial	**300** [k] Group A 200 (81.5:18.5) Group B 100 (75:25)	58.7 ± 12.1 60.1 ± 13.2	AMI	-	Group A vs. Group B **Arrhythmia** 22 vs. 24 (11 vs. 24) VT/VF in first day 8 vs. 4 (4 vs. 4) VT/VF in second day 0 vs. 3 (0 vs.3) New LBBB 2 vs. 3 (1 vs. 3) New RBBB 3 vs. 3 (1.5 vs. 3) 2nd degree AV-block 1 vs. 2 (0.5 vs. 2) 3rd degree AV-block 8 vs. 4 (4 vs. 4) AF 0 vs. 5 (0 vs. 5) **Pulmonary edema** 1 vs. 3 (0.5 vs. 3) **Cardiogenic shock** 2 vs. 2 (1 vs. 2) **GI bleeding** 2 vs. 0 (1 vs. 0) **Hypotension** 89 vs. 30 (44.5 vs. 30) **Ischemic CVA** 1 vs. 0 (0.5 vs. 1) **Hemorrhagic CVA** 1 vs. 0 (0.5 vs. 0) **Allergic reaction** 0 vs. 1 (0 vs. 1) **In-hospital mortality** 5 vs. 8 (2.5 vs. 8)	**SK regimen;** Hypotension was higher in Group A	-	**DC** 1; Generalized allergic reaction **Symptomatic therapy** 1; Hypotension (by rapid normal saline infusion)
14	Moghadam B, et al. 2013 (29)	Cross-Sectional Prospective	**100** (24:76)	**61.24±11.08**	AMI	-	**Total 232** [h] **Cardiovascular** 14[e] (62); PVC 46(19.8) VT 7(37) VF 1(0.4) SB 17(7.3) IVR 25(10.7) AVB 5(2.1) Hypotension 44(18.9) **Bleeding** 13(5.6); Subcutaneous bleeding 13(5.6) **GI** 44(18.9); Nausea /vomiting 44(18.9) **Allergic reactions** 30(12.9); Chill 23(9.9) Fever 7(3)	In spite of non-significant association between ADRs (total) and age, SB was higher in younger, Hypotension and N/V were higher in older	Age Gender	-

M; Male, F; Female, AMI; Acute Myocardial Infarction, GI; Gastrointestinal, ICH; Intracranial Hemorrhage, SK; Streptokinase, AST; Aspartate Transaminase, ALT; Alanine Transaminase, ALP; Alkaline Phosphatase, IV; Intravenous, DC; Discontinue, HTN; Hypertension, STEMI; ST Segment Elevation Myocardial Infarction, VT; Ventricular tachycardia, IHD; Ischemic heart disease, PT; Prothrombin time, CVD; Cardiovascular Disease, PVC; Premature Ventricular Contraction, PAC; Premature Atrial Contraction, SB; Sinus Bradycardia, N/V; Nausea And Vomiting, VF; Ventricular Fibrillation, AIVR; Accelerated Idioventricular Rhythm, AVB; Atrioventricular Block, IVR; Idioventricular Rhythm, LBBB; Left Bundle Branch Block, RBBB; Right Bundle Branch Block, AV; Atrioventricular, AB; Atrial Block

a We just mentioned the events with higher incidence in the SK+ vs. SK- group. There was no significance reported between these 2 groups. b In patient with hypotension after right ventricular infarction. c Significantly different between 2 groups. d They lowered HTN with antihypertensive drugs first. e H2 blocker and/or Corticosteroids administered in some of the patients before SK. f The study result did not show significant difference in ADRs between patients who received SK with hydrocortisone and those who received SK alone, so, only data from patients who did not receive hydrocortisone with SK is presented. g In this study the frequency of cardiovascular ADRs (only arrhythmia observed) was reported separately from other ADRs without clarifying the co-occurrence of these two classes of ADRs in patients. h In these studies proportion of events are reported as number of event per total events (instead of total patients). i These studies evaluated the ADRs due to all of the CV medications used in CCUs. Only data regarding streptokinase are presented in the table. j Group A patients received accelerated regimen of SK (1.5 MIU, IV infusion over 20 min) and Group B patients received conventional regimen of SK (1.5 MIU, IV infusion over 60 min). k It was reported that 95 (43%) of all study patients developed complications during 24 hours of SK therapy.

administration was not mentioned (1, 31, 36-37).

Among the studies which the age of the recruited patients were reported, all of them except one were conducted on adult patients. The mean age of patients in half of the included studies was more than 55 years. Only in one study, SK was used in infant and young children (48.5% were under 12 month old) (27).

SK dosing regimen

Among the studies on patients with AMI, five studies mentioned dosing regimen of SK as 1.5 MIU, IV infusion, over 45-60 minutes (23, 25-26, 28, 35). In four other articles on AMI patients, the authors noted the dose 1.5 MIU, but the infusion rate was not addressed (22, 29, 34, 39). One of the double blind RCTs on AMI patients aimed to compare the efficacy and safety of accelerated regimen (1.5 MIU, IV infusion over 20 minutes) with the conventional regimen (1.5 MIU, IV infusion over 6 minutes) of SK (33). In three other studies on AMI patients, neither doses nor the duration of infusion of SK were mentioned (24, 30, 38).

Dosing regimens of SK were mentioned in two studies that used this medication for the treatment of thrombosis. In the study on patients with acute thrombosis of mechanical prosthetic valve SK was administered with 250000 IU IV bolus that followed by 100000 IU/h for 48-72 hours (32). Dosing regimen of SK in the study by Noori et al., for treatment of femoral artery thrombosis following catheterization in infant and children, was 2000 IU/Kg, IV bolus over 20-30 minutes, then followed by 1000 IU/kg/h IV infusion, until pulse recovery, then they tapered it off over 2-3 hours (27).

SK Formulation and brand name

In only 5 of the studies the manufacturer and/or brand name of the SK were pointed. Among them, 3 studies used SK manufactured by Heber Biotec, Cuba (Heberkinasa®) (26-27, 38) and one study reported Streptase® as their available SK brand (35). The remaining study was a double blind RCT that as mentioned above was conducted to compare the safety and efficacy of Streptase® with Heberkinasa® (a recombinant formulation of SK) (24).

ADRs descriptions

Only in three studies that were conducted by pharmacists, the WHO definition for ADR and its severity (1, 31, 37) were used. Additionally, causality and preventability of ADRs were only assessed in two of the above-mentioned articles based on WHO criteria and Schumock and Thornton questionnaire (1, 31, 40). In the study by Garjani et al., ADRs were categorized into mild if they resolved spontaneously, moderate if they resolved with symptomatic and supportive therapy and severe if required SK discontinuation and appropriate management (38). Although it was proposed in the method section of two studies to categorize side effects according to their severity, they did not report them according to the predefined classification (24, 33).

Many studies did not report the total number of adverse events along with the total number of patients who developed ADRs.

Shalviri et al., in their study that aimed to describe quantitative methods for detecting new drug safety signals noted that from March 1998 to January 2005, 240 cases of rigors due to SK were reported to the Iranian Pharmacovigilance Center. This drug was the leading agent in the number of reports (37).

In another study, Shalviri et al., presented the data of activities of the Adverse Drug Reaction Monitoring Center in Iran from 1998 to 2008. In this study, SK was ranked as the third most frequent cause of ADRs reported to this center from all over Iran. They mentioned that from the total number of 17967 reports, 576 cases were due to SK. However, it should be noted that some of the reports (1094 reports) were categorized as medication errors and the number of SK reports due to medication errors was not described in their study(36).

Mohebbi et al., evaluated the ADRs due to all of the cardiovascular medications in 677 patients during an 8-month study and found that SK was responsible for the highest rate of ADRs (59.26%). They reported 35 serious adverse reactions in total of 189 ADR events, among them there were four cases with due to SK. Fortunately, all of the patients recovered finally. (1).

In a 16 months period study conducted by Karimzadeh et al., on 740 patients in the coronary care unit (CCU), they recorded 70 ADRs. In seven cases, SK was suspected to be the causative agent. SK was placed as the 3rd most frequent cause of serious ADRs (10.91%) following digoxin and atenolol in this study (31).

Among complications of SK in patients with AMI, cardiovascular events were the most frequently observed and reported ADRs. Arrhythmia and hypotension were two most commonly reported cardiovascular complications following SK therapy (22-26, 28-30, 33-35). Premature ventricular contraction (PVC) was the leading arrhythmia in the studies that described types of arrhythmias in detail (22, 28-29, 33-34).

Bleeding was reported in 14 studies and was a commonly observed adverse event following cardiovascular ADRs (1, 22-25, 27-34, 38). Minor bleeding (epistaxis, hematuria, local blood oozing) and mild to moderate hematoma were most frequent reported ADRs in two studies that used SK for mechanical valve thrombosis in adult and femoral artery thrombosis in infants and young children (27, 32).

In the study by Noori et al., 24 patients out of 33 infants and young children did not develop any ADR. Other than local blood oozing and hematoma, three bleeding events were reported in this study. However, the site and severity of these bleedings were not mentioned in the paper. They

administered H2 blocker and corticosteroid before SK administration to half of their patients as prophylactic measures, in whom only local oozing and mild hematoma were developed. Lack of more data about this subgroup of patients preclude further conclusion. It should be noted that some of the patients in this study received SK after failure of initial heparin administration. Number of patients who received heparin before SK and the probable association of reported ADRs with prior heparin administration were not reported in this paper (27).

Gastrointestinal (GI) bleeding was reported in eight studies (1, 23, 28, 30-31, 33-34, 38). Intracranial hemorrhage (ICH) and hemorrhagic cerebrovascular accident were reported in six studies (22-23, 30, 32-34) that led to death in two of cases (22, 32). In the study by Hakim et al., ICH occurred 48 hours after treatment with SK in one patient and led to death (32).

Hakim et al. also reported two cases of transient systemic embolism (renal, cerebral), among complications of treatment with SK in patients with acute thrombosis of mechanical prosthetic valve (32).

Seven studies reported allergic reactions to SK (22, 24-25, 27, 29, 33-34). Frequency of the reported allergic reaction ranged from 1 to 32.2% of all events. The lowest frequency was reported in the study by Ghaffari et al., in which, they only pointed one case of allergic reactions that led to SK discontinuation. However, it is not clear whether other cases with allergic reactions were developed which did not result in SK discontinuation in this study (33). By excluding this article, the frequency of allergic reactions reached 11.3-32.2%. The most repeated allergic reactions in studies were chills and fever and ranged between 11-14% of all of the ADRs. Only one study mentioned anaphylactic reaction due to SK (27).

Garjani et al., studies the ADRs caused by SK in 3 consecutive years from 1999 to 2001. The frequency of ADRs was 10.47, 10.74 and 50% in 1999, 2000 and 2001 respectively and was significantly higher in 2001. The authors attributed the higher ADRs in these patients to the source of SK that was Heberkinase. The most frequent ADRs in 1999, 2000 and 2001, were GI bleeding, nausea-chill and allergic reactions like chill and fever respectively. Most of the ADRs during the study period were of moderate severity and were managed with symptomatic therapy. In 1999 and 2000 severe ADRs like hypotension and GI bleeding were considerable. In 2000, 38.55 of all of the ADRs were severe and required drug discontinuation while, 90.6% of ADRs in 2001 were moderate (38).

The study by Noogh was the only study that evaluated the effect of SK on liver enzymes. He reported that in 46.6 % of patients who received SK, liver enzymes increased significantly after 48 hours, although this elevation did not result in jaundice, the enzymes were close to reach to 2-3 fold upper limit of normal . He found that changes in transaminases, slowly resolved and reduced to the normal value by the 7th day after patients discharge and one month after SK injection they all backed to normal. Additionally, no changes in total or direct bilirubin was noted due to SK utilization (26).

In the only case report that was included in our study, Eshraghian et al., described a case of Guillain-Barre syndrome 12 days after SK therapy for the treatment of AMI in a 70 years old obese man. He discharged from the hospital with partial recovery (muscle power returning to 3 of 5 in all extremities) (39).

Complications of ADRs

Death was reported as a measure of clinical outcome and complications of patients who were treated with SK in many of the studies, however, causality of SK was not assessed and mentioned in most of them. Salarifar et al., reported that among 12 patients who died during hospitalization one case of death was attributed to the ADR of SK; however, the ADR and the SK formulation were not mentioned (24). In another study by Shemirani et al., incidence of neurological symptoms was evaluated in 300 elderly patients who received SK for the treatment of AMI. They just reported 66 deaths (22%), which 37 (56.06%) cases among them were due to arrhythmia and recurrent MI and 29 (43.93%) were because of hypotension and bradycardia. They did not mention whether these events were associated with SK or not(35).

As mentioned above among six cases of ICH that were reported in studies, two patients died because of this ADR (22, 32). Shojaie et al., also reported a 82 years old patient who developed ICH and died during hospitalization (22). In terms of ADR outcomes, one case of mortality due to GI bleeding was reported by Karimzadeh et al., in a 67-year old man after receiving SK for the treatment of AMI(31).

Management of ADRs

In different studies, various strategies from symptomatic therapy and supportive care to medication discontinuation were applied to manage ADRs. Salarifar et al., reported 6 cases of life-threatening ADRs that necessitated discontinuation of SK, however the symptoms of patients and the SK brands were not clarified (24). The patient who developed Guillain-Barre syndrome following SK underwent plasmaphresis, (five times, every other day) and received 5 doses of IVIG (39).

Associated Factors

Among evaluated associated factors with SK ADRs, only age and SK regimen were reported significant in the studies (22, 33).

The roll of the source of SK and its brand on the frequency of complications during the infusion period and within 24 hours was assessed in one study and no

differences in the ADRs was noted (24). In another study which aimed to compare the ADRs between patients who received hydrocortisone along with SK and those who did not receive it no significant differences was reported (28).

Age:

Moghadam et al., reported that there were no significant association between ADRs and patients' age. However, they found that sinus bradycardia in younger patients and, hypotension and nausea and vomiting in older patients were observed significantly different among groups (29).

In a study performed by Shojaie et al., Hypotension (53.3% vs. 27.1%, P=0.02) and sinus bradycardia (26.7% vs. 8.6% P=0.04) were cardiovascular ADRs with significantly more frequency in older (>70 yrs.) than younger patients (<70 yrs.) (22). The frequency of other cardiovascular ADRs was not different significantly between two groups.

SK regimen:

In one RCT, the role of SK infusion rate was evaluated in the frequency of ADRs along with the efficacy. They found that the frequency of hypotension was higher in patients who received accelerated regimen (44.5% vs. 30%; P = 0.02). They defined "SK induced hypotension" as more than 20 mmHg decrease in systolic blood pressure within 20 minutes of starting the treatment (33).

Preventability

Mohebbi et al., reported the preventability of ADRS in general and did not specify it regarding ADRs caused by SK (1). However, Karimzadeh et al., reported that among serious ADRs due to SK, 1 case of GI bleeding and 1 case of hematuria which were attributed to drug-drug interaction, were preventable (31).

Discussion

Nowadays, fibrinolytic agents with superior efficacy compared with streptokinase are available in a number of countries for the treatment of AMI [38], but, the limitations in availably and higher prices are two important factors that preclude their utilization in some developing countries like Iran and this makes the physicians to use SK widely instead. It should be noted that in countries like US, SK is not available. Therefore, this review can be interesting for health care providers in developing countries. Most of the studies included in this review were conducted in AMI patients followed by treatment of thrombosis. None of them was investigating SK administration in patients with ischemic stroke. This can be explained by considering the guidelines which does not recommend SK in this setting due to considerable adverse reactions particularly hemorrhage(41).

As it was expected, the well-known ADRs of SK were also detected in Iranian studies.

SK is not a fibrin specific and is an immunogenic agent (42). Therefore, one of the concerns regarding SK safety is the allergic reactions. In seven studies in Iranian population the allergic reactions were reported (22, 24-25, 27, 29, 33-34). Other studies reported allergic reactions most of which included chills and fever. In a review article by Rogers et al. fever was reported to occur in 15-25% of patients who received SK, which is similar to the range of this ADR in our included studies (11.3-32.2%). They also reported that allergic skin reactions occurred in 2-6% of patients, but only in one of our studies, urticaria was reported in 4.4% of patients. It seems that applying better methods in purifying SK can decrease the incidence of allergic reactions with this medication (43)

Only Noori et al., reported cases of anaphylaxis due to SK among our studies (27). This ADR was reported to be rare in the review by Rogers et al. (43). In "Global Utilization of Streptokinase and Tissue Plasminogen Activator (t-PA) for Occluded Coronary Arteries (GUSTO-I)" trial, allergic and anaphylactic reactions were noted in 5.7% and 0.6% of patients who received SK monotherapy respectively (44). Both of these events were less frequent than what is presented in Table 1. Allergic reactions in International Study of Infarct Survival (ISIS-2) and ISIS-3 were lower than GUSTO-I with the incidence of 4.4% and 3.6% respectively which was attributed to the strict observations in GUSTO trial (44). Unfortunately, our studies did not report the outcome of these patients.

Many of the clinical trials reported minor or major bleeding as an ADR of SK administration (43). Bleeding is an important safety issue in patients who undergo treatment with SK. It has also been proposed that one of the reasons for using SK less frequently than indicated can be the concerns regarding complications, in particular hemorrhagic events (43). In 14 articles in our review, bleeding from various sites was one of the ADRs (1, 22-25, 27-34, 38).

It was pointed that minor bleeding following SK administration was primarily oozing from invasive procedure sites. Other major or minor bleeding occurred at retroperitoneal, GI, and genitourinary sites (43). In our studies the most frequent reported bleeding site was GI in 5 studies, followed by epistaxis and hematuria both of which were reported in 3 studies. There was 1 case of death due to bleeding in our included studies (31). In the study by Rogers et al. only 2 cases (0.24%) of death due to hemorrhagic complications of SK was observed among the patients from different studies (43).

All of our studies only mentioned the bleeding site and despite of providing definitions for severity of bleeding in some of the method sections of the studies, (24, 33) none of them addressed it in their results.

Intracranial hemorrhage (ICH) and hemorrhagic cerebrovascular accident were reported in six Iranian studies (22-23, 30, 32-34) which led to death in two patients (22, 32). Although, due to the heterogeneity in the studies we could not sum these ADRs but the approximate

frequency extracted from 5 studies, was calculated to be 0.93% (8 patients from 860 patients who received SK) in 5 studies (23, 30, 32-34) which is close to what Rogers et al. reported in their review (8 of 874 patients, 0.9%).

Reversible hepatic damage was another ADR which was reported infrequently in the study by Rogers et al (43). Only in one study in our review, the authors assessed the effect of SK on liver function tests. They found that rise of liver enzymes was reversible and resolved after almost 7 days (43). Among the factors that have been evaluated as a risk factor in patients with ADR, age was the factors assessed in four studies. Shojaie et al., categorized patients in two groups of younger and older than 70 years old(22). They found that hypotension and sinus bradycardia were significantly more common in the older group. In contrast in another study by Moghadam et al., they found that sinus bradycardia was significantly more prevalent in younger patients (<60 years old). But their results was in accordance with Shojaie et al., regarding hypotension (29). Moreover, Shemirani et al., and Nasiri et al., did not find any significant association between patients' age and higher rate of any ADRs (28, 35).

In most of the studies included in this review, the authors did not assess the causality of the reported complications following SK administration. Thus, the judgment regarding the offending agent in these patients is challenging. This might be due to fact that similar cardiovascular events might happen with different causes, like MI itself or the concomitant therapies. For example, there are many similarities in the reported ADRs by Khani et al., in 2 group of patients with and without SK therapy (33).

Conclusion and limitation

The present review shows that Iranian patients who received SK are susceptible to the wide range of adverse effects. Among them, the most frequently reported ones were cardiovascular side effects (like arrhythmia and hypotension), bleeding and allergic reactions. To the best of our knowledge this is the first review that covered and gathered the published adverse effects of SK regimen in Iran. However, the limitation of this study is related to the presence of a few numbers of studies which specifically focused on detection of ADRs. Many of the studies lacked some of the data such as definition of ADRs, patient characterization in whom ADRs were documented, factors associated with ADR experience, and the management strategies when ADR was observed. Moreover, severity, causality and preventability assessment of ADRs were evaluated in limited studies.

References

1. Mohebbi N, Shalviri G, Salarifar M, Salamzadeh J, Gholami K. Adverse drug reactions induced by cardiovascular drugs in cardiovascular care unit patients. Pharmacoepidemiol Drug Saf 2010; 19: 889-94.
2. Laslett LJ, Alagona P, Jr., Clark BA, 3rd, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am Coll Cardiol 2012; 60: S1-49.
3. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet 1999; 353: 89-92.
4. Khalili D, Sheikholeslami FH, Bakhtiyari M, Azizi F, Momenan AA, Hadaegh F. The incidence of coronary heart disease and the population attributable fraction of its risk factors in Tehran: a 10-year population-based cohort study. PLoS ONE 2014; 9: e105804.
5. Talaei M, Sarrafzadegan N, Sadeghi M, et al. Incidence of cardiovascular diseases in an Iranian population: the Isfahan Cohort Study. Arch Iran Med 2013; 16: 138-44.
6. Nascimento BR, de Sousa MR, Demarqui F, Nogueira b, Ribeiro ALP. Risks and Benefits of Thrombolytic, Antiplatelet, and Anticoagulant Therapies for ST Segment Elevation Myocardial Infarction: Systematic Review. ISRN Cardiol 2014; 2014: 416253..
7. Ali MR, Salim Hossain M, Islam MA, et al. Aspect of Thrombolytic Therapy: A Review. Scientific World Journal 2014; 2014: 8.
8. Kumolosasi E, Wei WS, Wee CE. The use of thrombolytic agents in acute myocardial infarction (AMI) patients. Int J Pharm Pharm Sci 2013; 5(2):63-7.
9. Hermentin P, Cuesta-Linker T, Weisse J, et al. Comparative analysis of the activity and content of different streptokinase preparations. Eur Heart J 2005; 26: 933-40.
10. Kunadian V, Gibson CM. Thrombolytics and Myocardial Infarction. Cardiovasc Ther 2012; 30: e81-8.
11. Van de Werf F. Recommendations for an efficient and safe use of fibrinolytic agents. Bangkok Medical Journal 2014; 3.
12. Bizjak ED, Mauro VF. Thrombolytic Therapy: A Review of Its Use in Acute Myocardial Infarction. Ann Pharmacother 1998; 32: 769-84.
13. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. Qual Saf Health Care 2005; 14: 221-6.
14. Vahanian A. Thrombolytic therapy in Europe: current status. Eur Heart J 1996; 17: 21-7.
15. Spöhr F, Böttiger B. Safety of Thrombolysis during Cardiopulmonary Resuscitation. Drug Saf 2003; 26: 367-79.
16. Diwedi S, Hiremath J, Kerkar P, et al. Indigenous recombinant streptokinase Vs natural streptokinase in acute myocardial infarction patients: Phase III multicentric randomized double blind trial. Indian Journal of Medical Sciences 2005; 59: 200-7.
17. Jianjaroonwong V. The Efficacy and Safety of Streptokinase in the Treatment of patients with Acute myocardial infarction at Lumplaimat Hospital, Burirum Province. Medical Journal of Srisaket Surin Buriram Hospitals 2011; 22: 169-81.
18. Tatu-Chitoiu G, Teodorescu C, Dan M, et al. Efficacy and Safety of a New Streptokinase Regimen with Enoxaparin in Acute Myocardial Infarction. J Thromb Thrombolysis 2003; 15: 171-9.
19. Thanvi BR, Treadwell S, Robinson T. Haemorrhagic transformation in acute ischaemic stroke following thrombolysis therapy: classification, pathogenesis and risk factors. Postgrad Med J 2008; 84: 361-7.
20. Weinstein J. Treatment of myocardial infarction with intracoronary streptokinase: Efficacy and safety data from 209 United States cases in the Hoechst-Roussel registry. Am Heart J 1982; 104: 894-8.
21. Feizi A, Nasr A, Sanei H, Mikaili P, Amirpoor A, Ghasemi N. Effect of Streptokinase on Short-term Outcomes in the Acute Myocardial Infarction with ST-Segment Elevation. J Rep Pharm Sci 2014; 3: 85-9.
22. Shojaei M, Abdi MH. A Survey of the Side Effects of Intravenous Streptokinase in Patients Older than 70 Years with Acute Myocardial Infarction. Journal of Jahrom University of Medical Sciences 2009; 7: 7-14.
23. Shemirani H, Hashemi SH, Beiki O. Intracranial hemorrhage in normotensive and hypertensive patients receiving Streptokinase after decreasing elevated blood pressure. JRMS 2005; 10: 297-2.
24. Salarifar M, Sadeghian S, Abbasi A, et al. Efficacy of Two Streptokinase Formulations in Acute Myocardial Infarction: A Double-Blind Randomized Clinical Trial. J Teh Univ Heart Ctr 2009; 4(1): 29-34.
25. Saffari M, Samei A, Abdoli H, Isfahani MA. Clinical effects of Streptokinase in acute myocardial infarction. Kashan University of Medical Sciences Journal (Feyz) 2003; 6: 6-10.
26. Nough H. Effect of Streptokinase on Liver Function in Patients with Acute Myocardial Infarction. Journal of Rafsanjan University of Medical Sciences

2002; 2: 61-7.
27. Noori N, Rozati A. Streptokinase treatment for femoral artery thrombosis after cardiac catheterization in children. Iranian Journal of Pediatrics 2006; 16: 51-6.
28. Nasiri M, Rahimian B, Bashiri T, Salmalian F. Adverse reactions of streptokinase in patients with or without hydrocortisone injection. Journal of Urmia Nursing And Midwifery Faculty 2011; 9: 43-8.
29. Moghadam M, Zeighami R, Azimian J, Jahani-Hashemi H, Fotuhi M. Side Effects of Intravenous Streptokinase in Different Age Groups Patients with Acute Myocardial Infarction Armaghane-danesh 2013; 18: 910-7.
30. Khani M, Taherkhaney D. The Survey Of The Effects Of Streptokinase On The Patients Suffering From Inferior Wall Infarction Associated With Right Ventricular Infarction. Journal Of Zanjan University Of Medical Sciences And Health Services 2001; 9: 4-9.
31. Karimzadeh I, Namazi S, Shalviri G, Gholami K. Cardiovascular drug adverse reactions in hospitalized patients in cardiac care unit. African Journal of Pharmacy and Pharmacology 2011; 5: 493-9.
32. Hakim S, Samadikhah G, Gafari S, Alizadeh A. Fibrinolytic Therapy in Acute Thrombosis of Mechanical Prosthetic Valve. Journal of Ardabil University of Medical Sciences 2006; 6: 19-23.
33. Ghaffari S, Kazemi B, Golzari IG. Efficacy of a New Accelerated Streptokinase Regime in Acute Myocardial Infarction: A Double Blind Randomized Clinical Trial. Cardiovasc Ther 2013; 31: 53-9.
34. Fayazi S, Abdi MH, Sayadi N, Rostami S. Complications of intravenous Streptokinase therapy in acute myocardial infarction patients admitted to the cardiac intensive care unit. J Cardiovasc Nurs 2012; 1: 14-20.
35. Shemirani H, Saravi SFB. Incidence of Neurological Syndromes After Thrombolytic Therapy In Elderly Patients With Acute Myocardial Infarction. Journal of Isfahan Medical School 2008; 26: 85-91.
36. Shalviri G,Valadkhani M, Dinarvand R. Ten years pharmacovigilance activities in Iran. Iranian J Publ Health 2009; 38: 162-6.
37. Shalviri G, Mohammad K, Majdzadeh R, Gholami K. Applying quantitative methods for detecting new drug safety signals in pharmacovigilance national database. Pharmacoepidemiol Drug Saf 2007; 16: 1136-40.
38. Garjani A, Abedinogli K, Shamsmohammadi M, Salimnejad M, Maleki N. The Study Of Adverse Drug Reaction To Streptokinase In Inpatients With Acute Myocardial Infarction In Shahid Madani Hospital For Cardiovascular Disease In Tabriz Between 1999 and 2001. Pharmaceutical Sciences 2005; 25-8.
39. Eshraghian A, Eshraghian H, Aghasadeghi K. Guillain-Barre syndrome after streptokinase therapy for acute myocardial infarction. Intern Med 2010; 49: 2445-6.
40. Schumock G, Thornton J. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992; 27: 538.
41. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2013; 44: 870-947.
42. Ghosh M, Pulicherla K, Rekha V, Rao GV, Rao KS. A review on successive generations of streptokinase based thrombolytic agents. International Journal of Pharmacy and Pharmaceutical Sciences 2012; 4(3):38.
43. Rogers LQ, Lutcher CL. Streptokinase therapy for deep vein thrombosis: a comprehensive review of the English literature. Am J Med 1990; 88: 389-95.
44. Tsang TSM, Califf RM, Stebbins AL, et al. Incidence and Impact on Outcome of Streptokinase Allergy in the GUSTO-I Trial. Am J Cardiol 1997; 79: 1232-5.