

Ready-to-Use Injection Preparations versus Conventional Reconstituted Admixtures

Economic Evaluation in a Real-Life Setting

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Abstract

Objective: To measure, in a real-life setting, the benefits of using ready-to-use (RTU) injection preparations compared with conventional reconstituted admixtures (Admix) in terms of cost savings.

Design and perspective: An economic model was developed, based on a randomised study. The perspective of the economic evaluation was that of the hospital administration. A microcosting approach was used to determine costs.

Setting: Department of Cardiac Surgery at the Charleroi University Hospital in Belgium.

Study participants: Fifty-eight patients undergoing cardiac surgery under cardiopulmonary bypass were randomised to Admix dobutamine or to the RTU dobutamine group and were followed up during 24 hours after initiation of dobutamine therapy.

Main outcome measures and results: Nursing time was reduced by 32% in the RTU group compared with the Admix group. Material cost was also reduced and the overall cost savings in the RTU group amounted to a 60% reduction in the cost of the conventional Admix process ($p < 0.001$). When drug cost was included in the equation, cost savings varied from 1.60 euros (EUR) to EUR21.40 per patient depending on dosage. There was no difference between the two groups in terms of safety and efficacy. A user satisfaction survey showed that medical staff especially welcomed improved ease of preparation and potential for prevention of errors and risks of handling.

Conclusion: This study confirmed the potential for RTU forms to reduce nursing time associated with preparation and administration of intravenous admixtures and to enable overall cost savings.

In the US, the introduction of ready-to-use (RTU) medications has contributed to providing high quality intravenous (IV) preparations while sim-

plifying the process of delivering small volume parenterals. This system lends itself to more rapid availability of the dose and does not require that doses

be calculated or manipulated further by the medical staff. It may also free pharmacists and nurses to devote more time to other critical activities associated with the safety of intravenous drug delivery.

The RTU system facilitates efficiency, accuracy and safety: efficiency as it streamlines IV work flow, creating more time for clinical activities and patient interaction, reduces steps in IV preparation, eliminates admixing labour, assembly and supplies and reduces waste by providing extended shelf-life over admixed solutions;^[1-4] accuracy as it reduces the risk of medication errors, eliminates calculations during compounding and guarantees accuracy in IV medication labelling;^[5,6] and safety as it facilitates immediate use in emergency situations, ensures sterility and potency with a closed system and eliminates the need for further product manipulations.^[7] This system may increase acquisition costs, but the overall system costs are balanced by reduced preparation costs and wastage rates.

In Europe, such industrial ready-to-infuse drugs are almost not existent. Based on previous US experience showing the great advantages of this concept, there was a need to evaluate the potential benefits of such medications in the context of European hospitals. The purpose of this study was to measure in the real-life setting the benefits of RTU injection preparations as compared with conventional reconstituted admixtures in terms of cost savings. In addition, efficacy, safety and user satisfaction were also evaluated.

Methods

Patient Population and Treatments

This study was performed in accordance with the local Institutional Ethics Committee. All patients who participated gave their written informed consent. Patients were recruited in the department of Cardiac Surgery at the Charleroi University Hospital in Charleroi, Belgium. Patients were included if they had undergone cardiac surgery in the morning and if during the operation they were eligible for dobutamine treatment because of a low

cardiac output. Patients were excluded if they presented any contraindication found in the Summary of Product Characteristics for dobutamine^[8] or if their expected life duration was below or close to 1 day.

Dobutamine intravenous injection was initiated in the operating room using either the conventional preparation admixed from vials (Admix) by the medical staff and administered by syringe drivers or using the RTU dobutamine administered via an infusion pump. The precise dosage is described in table I.

Patients were randomised to the Admix or the RTU group prior to entry in the operation room. They were followed up until 24 hours after initiation of dobutamine therapy.

Economic Evaluation

The perspective of the economic evaluation was that of the hospital administration; costs are presented as 2001 values. The hypothesis was that efficacy and safety of both systems were comparable so that the main objective was to measure potential cost savings associated with the use of dobutamine RTU. For this same reason no long-term differences were expected between the two devices and the time frame for the economic evaluation was limited to the 24 hours following the first infusion of dobutamine.

The evaluation was focused on the direct costs

Table I. Study treatments

	Dobutamine admixture	Ready-to-use dobutamine
Availability	250mg/20ml single dose vials as a concentrate for infusion	Plastic Viaflex [®] plus containers 1000mg/250ml
Dosage	Determined by the physician; varies from 2.5 to 10 µg/kg/min depending on patient assessments and bodyweight	Determined by the physician; varies from 2.5 to 10 µg/kg/min depending on patient assessments and bodyweight
Preparation	Admixture	Ready to use
Administration	Syringe driver ^a + central venous catheter	Baxter's Colleague infusion pump + central venous catheter

a IVAC P6000 manufactured by Alaris Medical Systems, UK.

related to the preparation and the administration of dobutamine.

A microcosting approach was used to determine costs. For each patient, medical care used for preparing and initiating the first cycle of dobutamine was precisely documented. When extra cycles were needed for a patient, it was assumed that medical care consumption for these further cycles would be the same as for the first cycle.

A time-and-motion study, supplemented by a work-sampling study (time associated with pump programming was re-evaluated outside the trial without any real patients being involved), was performed to evaluate labour time associated with collecting, preparing and administering the drug. Preparation time started with collection of supplies and finished when the admixture was ready to infuse. Initiation time ran from the end of preparation to the time when the drug was administered to the patient and included calculating flow rates, attaching sets, and programming pumps. Consumption of all supplies associated with preparation and initiation was also recorded. Drug consumption was measured by the amount of dobutamine prepared in both groups.

Unit costs were abstracted from public databases. Disposables were costed using market prices before negotiation and not including taxes. The costs of using syringe drivers and infusion pumps were calculated from purchasing prices assuming 5 to 10 years' depreciation times depending on the medical department. Labour time was valued at the wage rate of the site. From the hospital perspective, there is no acquisition cost for Dobutrex®¹ since hospitals are reimbursed the full price by the Belgian public health insurance.

In order to facilitate adaptation to other settings and countries, an economic model was developed that incorporates the broader perspective of the health insurance. In the model, the price of dobutamine RTU was assumed to be the same per unit of volume as the price of dobutamine Admix which, in Belgium, is 6.69 euros (EUR) for one 250mg/20ml bottle of Dobutrex® for inpatients

(2001 values). The model also allowed for varying the dosage of dobutamine as doses of dobutamine usually administered in the cardiac surgery and intensive care units where the study was performed may differ from the dosage in other settings.

Qualitative Survey

When each patient cycle was completed, the medical staff was required to document satisfaction with the products. The instruments used were visual analogue scales ranging from zero for the worst to ten for the best. Medical staff were asked to rate ease of preparation, time for preparation, prevention of risks of errors and prevention of risks of handling.

Statistical Methods

Statistical analyses were performed using the SAS V8 package. Continuous variables were compared using Student's t-test and categorical variables were compared using either Wilcoxon's non-parametric test or the standard chi-square as deemed appropriate. Cost variables were compared using bootstrap t-tests.^[9]

Results

Efficacy and Safety

A total of 56 patients were recruited, with 28 in each group (table II). Groups were well balanced for age, sex ratio, weight and health status. There were slightly more females in the RTU group, although the difference was not statistically significant ($p = 0.19$). This minor imbalance accounts for the difference in mean weight.

All 56 patients received dobutamine for low cardiac output at emergence from cardiopulmonary bypass. Dobutamine was administered at the mean dose of 3.9 $\mu\text{g/kg/min}$ [standard deviation (SD) 2.5] in the Admix group and at 5.0 $\mu\text{g/kg/min}$ (SD 2.2) in the RTU group ($p = 0.10$). The duration of dobutamine administration was similar in both groups, with a mean of 16 hours and 29 minutes (SD 5 hours 28 minutes) in the Admix group versus

¹ The use of the trade name is for product identification purposes only and does not imply endorsement.

Table II. Population characteristics

Characteristic	Dobutamine admixture (n = 28)	Ready-to-use dobutamine (n = 28)	P-value
Age (y) [SD]	67.2 [10.4]	64.0 [11.5]	NS
Male/female	24/4	20/8	NS
Weight (kg) [SD]	80.7 [16.8]	77.1 [13.7]	NS
Clinical examination at inclusion			NS
Normal	15	16	
Abnormal	13	12	

NS = not significant; SD = standard deviation.

17 hours and 8 minutes (SD 4 hours 57 minutes) in the RTU group ($p = 0.65$).

Efficacy was monitored through periodic assessments of diastolic and systolic blood pressure and pulse rate. Blood pressure and pulse rate figures were collected from time zero until 24 hours after initiation of dobutamine therapy. There was no difference between the two groups of patients in terms of systolic ($p = 0.42$) and diastolic ($p = 0.58$) blood pressure nor in terms of pulse rate ($p = 0.28$). Safety was similarly unaffected by the type of device used to prepare and administer dobutamine (table III; $p = 0.33$ for the number of patients with at least one adverse event). Nineteen patients out of 56 (34%) experienced at least one adverse event possibly or probably related to study treatment. Only three of these patients experienced at least one serious adverse event. The most frequent adverse events were pulmonary infections, haemorrhage, atrial fibrillation and congestive heart failure.

Costs

Table IV presents the costs associated with collection of the material, preparation and administration of intravenous dobutamine. To estimate 24-hour medical care consumption and costs, the data collected during the first preparation cycle of dobutamine was multiplied by the total number of preparation cycles. There were 1.57 preparation cycles for Admix dobutamine on average versus only 1.00 for RTU dobutamine. In the RTU group, labour time was on average lower than in the Admix group (85 seconds). Time spared on the prepara-

tion phase using RTU was somewhat offset by a longer time spent on initiating the infusion but the balance remained favourable for RTU. The time saving was 85 seconds per patient ($p < 0.01$) or 32% of medical staff time, which translates into cost savings of EUR0.45 per patient.

The administration of Admix requires systematically the use of a 50ml syringe, a needle, a bag of physiological serum and a connector whereas the preparation of RTU requires only a preparation kit. Admix was administered using a syringe driver while RTU was administered using an infusion pump. Although infusion pumps were more expensive than syringe drivers, the overall cost of material needed for the preparation and the administration of RTU was lower than for Admix, with cost savings of EUR2.92 per patient.

When all costs were summed up, savings showed at every step for the RTU form resulting in an overall cost of EUR2.26 per patient versus EUR5.63 per patient in the Admix group ($p < 0.001$). Costs were reduced by EUR3.37 per patient (95% confidence interval: -EUR4.42 to -EUR2.48) or 60% by using RTU instead of conventional Admix.

Economic Model

Results of the economic model are presented in table V which shows the difference in costs per patient between Admix and RTU when drug cost is incorporated in the calculation and dosage of dobutamine is variable. While on average 1.57 vials of Admix dobutamine were used in this study, up to four and even eight vials of Admix dobutam-

Table III. Incidence of adverse events

Adverse event	Dobutamine admixture (n = 28)	Ready-to-use dobutamine (n = 28)
Atrial fibrillation	5	5
Acute renal failure	1	0
Infection	4	4
Haemorrhage	2	2
Respiratory distress syndrome	1	0
Heart failure	0	2
Myocardial infarction	0	1

Table IV. Medical care consumption and costs

	Dobutamine admixture	Ready-to-use dobutamine
Labour time		
First preparation cycle		
material collection	24 sec	5 sec
preparation	1 min 31 sec	54 sec
initiation	54 sec	1 min 57 sec
Number of preparations	1.57	1.00
Total labour time	4 min 22 sec	2 min 57 sec
Labour cost		
Hourly wage rate	EUR17.85	EUR17.85
Total labour cost	EUR1.32	EUR0.87
Materials (quantity; unit cost)		
50ml syringe	1.57/patient; EUR0.35	
Drawing needle	1.57/patient; EUR0.02	
Bag of NaCl 0.9% (100ml)	1.57/patient; EUR1.36	
Connector	1.57/patient; EUR0.59	
Syringe driver	1 day; EUR0.67	
Preparation kit		1/Viaflex®; EUR0.36
Infusion pump		1 day; EUR1.03
Number of vials/Viaflex®	1.57	1.00
Total material cost	EUR4.31	EUR1.39
Labour cost + material cost	EUR5.63	EUR2.26

EUR = euros.

ine may be used for a single patient in other hospitals. The model shows that in all cases, with the lowest RTU dosage, there would be overall cost savings no matter the number of bottles of Admix dobutamine usually administered of at least EUR1.20 per patient and up to EUR12.50 per patient. It also shows that cost savings may be further improved by selecting the appropriate dosage of RTU. For example, if the usual dose of Admix dobutamine is four bottles per patient, the optimal choice for the type of RTU would be the 1000mg/250ml dosage. Cost savings would be higher than for lower dosage RTU forms because the 1000mg/250ml RTU would not need to be replaced thus saving precious nursing time. By selecting the appropriate RTU dosage, potential cost savings would range

between EUR1.60 and EUR 21.40 per patient. Table V may be used as a tool for pharmacists to select the optimal dosage of RTU they will order from the pharmaceutical company.

The calculations behind the economic model that was developed based on the results of the trial are detailed in table VI. As an example, the costs of administering the total dose of 250mg, 500mg, 750mg or 1000mg of dobutamine to one patient using either Admix or RTU 500mg were compared. The cost of administration included the cost of nursing staff, material cost and drug cost. The calculation further reinforces the fact that the RTU form is cost saving as compared to the Admix form when the amount of drug used is comparable. Cost savings result because of a lower material cost and because the RTU form allows for a longer administration time and thus fewer preparation cycles.

User Satisfaction

User satisfaction was very good on average for both groups (figure 1). Medical staff welcomed the introduction of the RTU form, citing ease of preparation, potential benefits in terms of prevention of errors and of risks of handling, and time savings. The only drawback they noted was the administration process which required long and unusual programming of the infusion pump.

Table V. Cost savings (euros) per patient per day associated with the use of ready-to-use (RTU) dobutamine compared with dobutamine admixture

No. of dobutamine vials needed per patient	RTU dosage		
	250 mg/ 250ml	500 mg/ 250ml	1000 mg/ 250ml
1	-1.60		
2	-3.10	-4.70	
3	-4.70	+1.10 ^a	-1.20
4	-6.30	-8.80	-11.00
5	-7.80	-3.00	+8.10 ^a
6	-9.40	-12.80	-1.70
7	-11.00	-7.00	-11.60
8	-12.50	-16.90	-21.40

a Cases when the cost of RTU would be higher than the cost of dobutamine admixture.

Table VI. Sample cost calculations

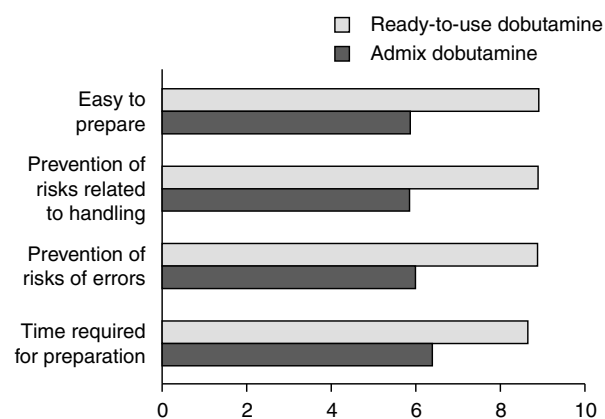
No. of dobutamine vials needed per patient	Cost component	Dobutamine admixture		Ready-to-use dobutamine (500mg)	
		quantity	unit cost (euros)	quantity	unit cost (euros)
2	Labour	5 min 38 sec	17.85/hr	2 min 56 sec	17.85/hr
	Material	2 sets	2.32	1 set	0.36
	Syringe or pump	1	0.67	1	1.03
	Drug	2 vials	6.69	1 Viaflex®	13.39
	Total cost	20.37		15.65	
3	Labour	8 min 27 sec	17.85/hr	5 min 52 sec	17.85/hr
	Material	3 sets	2.32	2 sets	0.36
	Syringe or pump	1	0.67	1	1.03
	Drug	3 vials	6.69	2 Viaflex®	13.39
	Total cost	30.22		31.30	
4	Labour	11 min 16 sec	17.85/hr	5 min 52 sec	17.85/hr
	Material	4 sets	2.32	2 sets	0.36
	Syringe or pump	1	0.67	1	1.03
	Drug	4 vials	6.69	2 Viaflex®	13.39
	Total cost	40.07		31.30	

Discussion

This prospective randomised study provided evidence that in the real-life setting RTU injection preparations offer significant benefits over conventional reconstituted admixtures in terms of time and cost savings and in terms of user satisfaction. In addition, efficacy and safety were also monitored and proved to be comparable.

While this study was conducted in the context of a hospital in Belgium, it may be anticipated that the savings identified will likely be of the same type in other contexts and other countries. Other studies have evaluated the potential benefits associated with the use of RTU preparations. Detournay et al.^[10] have observed cost savings of EUR0.23 per injection in the context of five European hospitals in five different countries. The design of their study was more simple than the current study in that medical care consumption figures were drawn from a process model. Barber et al.^[11] studied prefilled injections of heparin in two London hospitals and found that nursing time for preparation and administration using prefilled syringes was reduced from 129 seconds to 68 seconds when compared with conventional systems. Aden^[12] in Germany estimated

that the use of prefilled forms could save up to 50% of the cost associated with intravenous injections. Other studies in Spain^[13] found results consistent with the present one; in particular, savings due to reduced wastage when using prefilled syringes were identified. The present study differs from previous ones in many respects. It was performed in a real-life setting, with patients undergoing a major surgical procedure receiving a continuous infusion that could last up to more than 20 hours.

**Fig. 1.** Users' satisfaction.

In the conditions of the present study, the annual savings can be estimated by multiplying the number of intravenous injection cycles performed on average through the year by the EUR3.37 per patient savings identified. With approximately 2000 vials of Admix dobutamine administered annually and assuming that an average 1.57 vials are needed for each patient, the annual savings for the hospital would be around EUR4300.

Valuation of cost savings due to reduced nursing time may be controversial. It may be argued that savings in nursing time may not translate into actual cost savings because it is unlikely that hospitals will actually make adjustments to nursing staff and thereby actually save money. However, the savings in labour time could be invested in other tasks especially at patients' bedside. Furthermore, even without valuing nursing time, cost savings were identified with the use of RTU forms. Savings in the present study would amount to EUR2.92 per patient, corresponding to approximately EUR3700 on an annual basis.

Labour time can be further reduced with the introduction of improved infusion pumps. The programming of the pumps used in this study proved especially awkward. A more user-friendly programme was further developed by the manufacturer. A work-sampling study was conducted with the staff that participated in the trial. Three operators were observed while they were running the initiation phase and time was measured for both the Admix with the syringe driver and the RTU with the new infusion pump. A total of ten measures for each operator and both systems were performed. Mean initiation time and standard deviation were 29 seconds (SD: 3.5) for the Admix versus 43 seconds (SD: 4.1) for the RTU. No significant difference between operators was observed. These times were significantly shorter than those measured during the trial. This observation can be explained by the fact that this work-sampling study was not performed in real-life conditions. These results provide further evidence that labour time associated with the use of RTU will be reduced as compared with Admix. Nursing time

saved would amount to 2 minutes 30 seconds per patient using the new infusion pump.

Conclusion

A RTU form of dobutamine was evaluated in a study performed in patients undergoing cardiac surgery in a major hospital in Belgium. The study was conducted in real-life conditions and the RTU form was compared with the usual Admix preparation and administration process. Safety and efficacy of the two systems do not differ significantly. The economic analysis conducted using these real-life observations showed that both the nursing time and the material costs for preparation and administration of dobutamine were significantly lower with the RTU form than with the Admix one. From the perspective of the hospital, overall cost savings per patient amounted to EUR3.37 which corresponds to a 60% reduction of the total cost. When the perspective of the healthcare system as a whole was taken, and drug cost incorporated in the equation, the results suggested a potential cost savings of at least EUR1.60 per patient and up to EUR21.40 per patient depending on the dose of dobutamine prescribed and on the dosage of RTU selected. A user satisfaction survey showed that medical staff especially welcomed improved ease of preparation and potential for prevention of errors and risks of handling.

Acknowledgements

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