Economics of Unfractionated Heparin: Beyond Acquisition Cost

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Despite numerous clinical trials demonstrating advantages of new anticoagulants, unfractionated heparin (UFH) is still used by a number of clinicians in the United States. The reason for this continued use of UFH is not superior efficacy, improved safety, or convenience, but low acquisition cost. However, several other costs associated with the use of UFH are often not considered. Appropriate economic analysis, which considers both cost and outcomes, has not demonstrated support for continued use of UFH. Its continued use based simply on lower cost is not justified by the literature.
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Despite the advances in injectable anticoagulants over the last 10 years, unfractionated heparin (UFH) is still used by practitioners for a large number of patients. Since the efficacy and safety of UFH are not superior (and in some cases are inferior) to newer agents, there is little clinical justification for the continued use of UFH. In addition, UFH does not provide convenient dosing, easy administration, or reduced laboratory monitoring compared with newer agents. With all the disadvantages associated with UFH, the reason for its continued use is the perceived low cost associated with this anticoagulant.

Basic Cost Components

The basic cost of UFH using therapeutic dosages is approximately $5/day. This amount generally represents the pharmacy acquisition cost of the drug. However, other direct costs associated with UFH are not incurred with the use of newer agents. These additional costs are for intravenous tubing, an intravenous catheter, an automatic pump, phlebotomy, and monitoring the activated partial thromboplastin time (aPTT). Thus, although the apparent cost of UFH for 5 days of treatment may be only $25, the total cost of the therapy would be 4–5 times that amount.[1–3]

A comprehensive cost calculation for any therapy involves not only the acquisition cost of the agent (and associated costs), but also the economic impact of the clinical outcomes in terms of efficacy and safety.[4] The comprehensive costs of treatment with UFH can be evaluated from trials that have collected this economic information.

Comparative Economics

One analysis estimated that the initial total cost of treating venous thromboembolism (VTE) with UFH is approximately $3400.[2] The total cost was derived from standard charges representing the initial hospitalization ($2796), physician fees ($271), and drugs and supplies ($335). Complications due to lack of efficacy or reduced safety of VTE therapy are associated with a significant increase in the cost of care.

Economic information abstracted from this analysis determined that the cost of recurrent VTE within 3 months ($3485) was similar to that of the initial hospitalization; the cost of pulmonary embolism ($6187) was almost twice

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as much. The financial impact of bleeding complications increased the cost of care by $499 for a minor bleeding episode and $1245 for a major one. The efficacy and safety of UFH compared with other anticoagulant treatment options appear to have a more significant impact on the overall cost of care in the management of VTE.

In another VTE cost analysis, treatment of uncomplicated deep vein thrombosis (DVT) cost $5561 initially and $8784 at the 6-month follow-up.[5] This analysis of the initial treatment of VTE[5] was slightly higher than that reported in the previous study[2]; however, the more recent analysis was conducted approximately 3 years later than the earlier one. Complications due to lack of efficacy or problems with safety of the anticoagulant significantly increased the cost of care. For example, the cost of treating a patient with DVT leading to pulmonary embolism was $9476 initially and $14,649 at 6 months. Treatment for patients with minor bleeding episodes was $7980 initially and $12,142 at 6 months. Major bleeding episodes were associated with the highest cost of care: $11,189 initially and $17,169 at 6 months for each VTE event. Management of these complications significantly affected the final cost of VTE treatment. Some meta-analyses have demonstrated increased complications with UFH compared with other alternatives.[6–8]

Several clinical trials have demonstrated the efficacy and safety of outpatient DVT therapy.[9–12] This treatment option also has significantly reduced overall costs for institutions. However, patients receiving UFH are not candidates for outpatient VTE management; therefore, institutions may incur an additional cost of $2000–3000/inpatient.[1, 2, 13–15] This missed opportunity for cost containment may be apparent in other anticoagulant bridging situations involving UFH. For example, patients requiring anticoagulation bridging for atrial fibrillation, ischemic stroke, valve replacement, or other surgical procedures may be eligible for more cost-effective outpatient therapy with low-molecular-weight heparins (LMWHs).

Unfractionated heparin for prevention of VTE is much less costly than it is for treatment of a VTE event. Subcutaneous UFH for prophylaxis does not require intravenous tubing, an intravenous catheter, an automatic pump, or aPTT monitoring. Costs associated with UFH injections administered 2–3 times/day by nursing staff are difficult to ascertain. Also, UFH prophylaxis has demonstrated inferior efficacy when compared with other options in a number of situations, usually in high-risk patients. Patients undergoing orthopedic surgery, experiencing trauma, or sustaining an acute spinal cord injury should not receive UFH for VTE prophylaxis due to a lack of efficacy.[16] Economic analyses have also demonstrated that a cost-efficacy tradeoff with UFH does not exist. In patients undergoing orthopedic surgery, clinical outcomes have been worse and costs higher with UFH administration.[17–19] Findings have been similar in trauma patients.[20]

The efficacy of VTE prophylaxis regimens is critical to an economic analysis. The rate of VTE in certain high-risk patient populations is higher with UFH prophylaxis than with other anticoagulants. As a result, the cost of care for these patients increases significantly. Once patients develop an initial DVT, their long-term costs will increase due to the high rate of recurrent DVT or postthrombotic syndrome.[21]

The efficacy and safety of UFH also greatly affect the costs of UFH in cardiac patients.[22] The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-wave Coronary Events (ESSENCE) trial evaluated adjusted-dose UFH compared with an LMWH in patients with unstable angina or non–ST-segment elevation myocardial infarction. In a review of the composite end point, patients receiving the LMWH enoxaparin demonstrated significantly less death, recurrent myocardial infarction, and recurrent angina than patients receiving UFH. Although the acquisition cost was less for UFH than LMWH, overall hospital costs were higher for patients receiving UFH versus LMWH ($12,620 vs $11,857).

At 30 days, total medical costs were almost $1200 more for patients treated with UFH versus LMWH ($14,357 vs $13,185, p=0.04). Total costs for patients receiving UFH were higher primarily due to lack of efficacy, as demonstrated by the increased rate of recurrent angina and need for further hospitalization. If drug acquisition costs alone were considered, the agent demonstrating greater clinical efficacy as well as cost-effectiveness (LMWH) may not be used.

In a review of anticoagulant management during percutaneous coronary intervention, data were recently released from the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial.[23] The economic ramifications of enoxaparin superiority to UFH (with consistent therapy) have yet to be determined.

Other Cost Considerations

As mentioned, several other costs are associated with UFH besides acquisition cost. Complications resulting from UFH therapy can significantly affect the overall cost of managing thromboembolic disease. For example, bleeding events can have a wide range of cost implications depending on the severity of the episode.[24] Development of a small hematoma may not have economic consequences. However, if a minor intervention is required, the additional cost may be close to $75. More severe bleeding events, such as intraperitoneal or retroperitoneal bleeding, can cost approximately $2000 to manage.

Heparin-induced thrombocytopenia is not only a clinically devastating complication of UFH, but a costly one as well. Some of the costs involved with the management of heparin-induced thrombocytopenia are laboratory diagnostic tests, prolonged hospitalization, and several days of treatment with either argatroban or lepirudin. The total cost associated with the treatment of this complication can average $8000–$10,000/patient.[25]

Some of the other costs associated with UFH are related to monitoring, such as the cost of the aPTT test and the time and personnel needed to perform the test. In addition, costs associated with the continuing calibration and standardization requirements of the aPTT due to the use of numerous aPTT reagents and UFH products have not been quantified.

Nursing care associated with UFH also has economic implications. Time spent for training in the use of UFH, giving multiple subcutaneous injections, adjusting pumps for dosage changes, and contacting physicians about dosage changes is substantial and often overlooked. Calculating the cost of nursing time devoted to the completion of these particular tasks can be difficult, and the current national nursing shortage makes these considerations especially relevant. The use of UFH also affects the time spent by pharmacists involved with inpatient anticoagulation services because it redirects time and resources that could be spent on other aspects of patient care.[26] Finally, medication errors associated with UFH therapy have a negative clinical and economic impact on the institution and overall health care system.

Conclusion

The low acquisition cost of UFH is a critical factor contributing to its continued use. Unfortunately, other economic consequences are often overlooked or ignored. When the costs associated with lack of efficacy, complications, inconvenience, and labor intensiveness are considered, the decision to use UFH is not justified. Recommendations of the Heparin Consensus Group to enhance the economic outcomes of anticoagulation therapy are provided in Appendix 1.

References

1. **O'Brien B, Levine M, Willan A, et al**. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. Arch Intern Med 1999;159:2298–304.
2. **Gould MK, Dembitzer AD, Sanders GD, Garber AM**. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a cost-effective analysis. Ann Intern Med 1999;130:789–99.
3. **de Lissovoy G, Yusen RD, Spiro TE, Krupski WC, Champion AH, Sorensen SV**. Cost for inpatient care of venous thrombosis: a trial of enoxaparin vs. standard heparin. Arch Intern Med 2000;160:3160–5.
4. **Mark DB, Hlatky MA**. Medical economics and the assessment of value in cardiovascular medicine: part 1. Circulation 2002;106:516–20.
5. **O'Brien JA, Caro JJ**. Direct medical cost of managing deep vein thrombosis according to the occurrence of complications. Pharmacoeconomics 2002;20:603–15.
6. **Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS**. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med 1996;100:269–77.
7. **Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM**. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. Ann Intern Med 1999;130:800–9.
8. **Dolovich LR, Ginsberg JS, Douketis JD, et al**. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000;160:181–8.
9. **Levine M, Gent M, Hirsh J, et al**. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996;334:677–81.
10. **Koopman M, Prandoni P, Piovella F, et al**. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. N Engl J Med 1996;334:682–7.
11. **Wells PS, Kovacs MJ, Bormanis J, et al**. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with home care injection. Arch Intern Med 1998;158:1809–12.
12. **Harrison L, McGinnis J, Crowther M, et al**. Assessment of outpatient treatment of deep-vein thrombosis with low-molecular-weight heparin. Arch Intern Med 1998;158:2001–3.
13. **Groce JB**. Patient outcomes and cost analysis associated with an outpatient deep venous thrombosis treatment program. Pharmacotherapy 1998;18(6 pt 3):175S–80.
14. **Dedden P, Chang B, Nagel D**. Pharmacy-managed program for home treatment of deep vein thrombosis with enoxaparin. Am J Health-Syst Pharm 1997;54:1968–72.

15. **Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G**. Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs. inpatient treatment with unfractionated heparin. Chest 2002;122:108–14.
16. **Geerts WH, Heit JA, Glagett GP, et al**. Prevention of venous thromboembolism. Chest 2001;119(1 suppl):132S–75.
17. **Hawkins DW, Langley PC, Krueger KP**. Pharmacoeconomic model of enoxaparin versus heparin for prevention of deep vein thrombosis after total hip replacement. Am J Health-Syst Pharm 1997;54:1185–90.
18. **Marchetti M, Liberato NL, Ruperto N, et al**. Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement. Haematologica 1999;84:730–7.
19. **Anderson DR, O'Brien BJ, Levine MN, Roberts R, Wells PS, Hirsh J**. Efficacy and cost of low-molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. Ann Intern Med 1993;119:1105–12.
20. **Devlin JW, Petitta A, Shepard AD, Obeid FN**. Cost-effectiveness of enoxaparin versus low-dose heparin for prophylaxis against venous thrombosis after major trauma. Pharmacotherapy 1998;18:1335–42.
21. **Prandoni P, Lensing AWA, Cogo A, et al**. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1–7.
22. **Mark DB, Cowper PA, Berkowitz SD, et al**. Economic assessment of low-molecular-weight heparin versus unfractionated heparin in acute coronary syndrome patients: results from the ESSENCE randomized trial. Circulation 1998;97:1702–7.
23. **Conceptis Technologies, Inc**. SYNERGY: enoxaparin as effective as heparin but bleeding may be an issue. Available from http://www.theheart.org /viewEntityDispatcherAction.do?primaryKey=525974. Accessed March 10, 2004.
24. **Hull RD, Paskob GE, Rosenbloom D, et al**. Treatment of proximal vein thrombosis with subcutaneous low-molecular-weight heparin vs. intravenous heparin: an economic perspective. Arch Intern Med 1997;157:289–94.
25. **Spinler SA, Dager W**. Overview of heparin-induced thrombocytopenia. Am J Health-Syst Pharm 2003;60(suppl 5):S5–11.
26. **Mamdani MM, Racine E, McCreadie S, et al**. Clinical and economic effectiveness of an inpatient anticoagulation service. Pharmacotherapy 1999;19:1064–74.

Appendix 1. Recommendations to Enhance the Economic Outcomes of Anticoagulation Therapy

1. A comprehensive economic evaluation of any anticoagulant should include drug cost, efficacy and safety, monitoring, administration, reimbursement, and length of stay.
2. Where appropriate, outpatient VTE management is preferred.